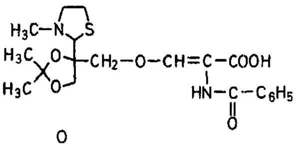
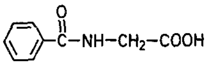
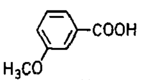
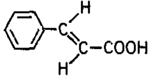
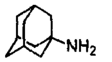
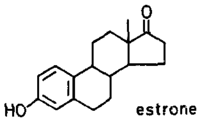
A Selective, Mild Cleavage of Trichloroethyl Esters, Carbamates, and Carbonates to Carboxylic Acids, Amines, and Phenols using Zinc/Tetrahydrofuran/pH 4.2–7.2 Buffer

G. JUST*, K. GROZINGER

Department of Chemistry, McGill University, Montreal, Canada

The utility of the 2,2,2-trichloroethyl blocking group for carboxylic acids is somewhat restricted, since a number of compounds are either unstable or recoverable with great difficulty only when the recommended solvents acetic acid[1,2], formic acid[3], or dimethylformamide[4] are used, whereas the procedure using activated zinc in boiling methanol[5] is not always applicable.

Table. Regeneration of Carboxylic Acids, Amines, and Phenols from 2,2,2-Trichloroethyl Carboxylates, 2,2,2-Trichloroethyl Carbamates, and Aryl 2,2,2-Trichloroethyl Carbonates, respectively

Acid, Amine, or Phenol	2,2,2-Trichloroethyl Derivative			Recovery [%] obtained with Zinc in Aqueous Tetrahydrofuran (Time required for cleavage)		
	Method[a]	Yield [%]	m.p. or b.p.	pH 4.2 (phosphate)	pH 5.5 (phosphate)	pH 7.2 (NH_4OAc)
	Ref.[10]	92	oil[10]	74 (10 min)	70 (10 min)	72 (10 min)
	B	98	m.p. 125–126°[b]	76 (10 min)	83 (10 min)	66 (10 min)
	A	74	b.p. 115°/20 torr[b]	84 (10 min)	80 (15 min)	76 (10 min)
	A	89	b.p. 112°/15 torr[b]	83 (10 min)	75 (10 min)	77 (30 min)
	Ref.[5]	97	m.p. 122–124° (Ref.[5], m.p. 123–124°)	86 (30 min)	96 (18 h)	96 (18 h)
 estrone	Ref.[5]	87	m.p. 139–141° (Ref.[5], m.p. 140–141°)	97 (4 h)[c]	12[d] (24 h)	16[d] (24 h)

[a] Methods A and B, see text.

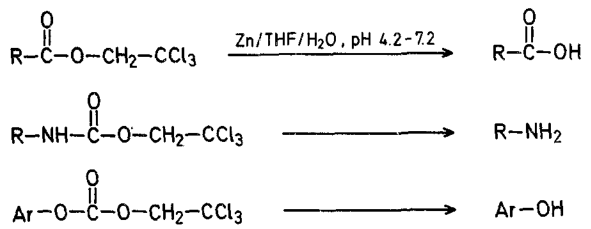
[b] This compound was characterized by I.R., ^{1}H-N.M.R., and microanalysis.

[c] This run was repeated and it took 6 h for cleavage.

[d] Balance consisted of unreacted trichloroethyl carbonate.

We have found that 2,2,2-trichloroethyl esters can be smoothly cleaved with zinc in 10 min at room temperature at pH 4.2–7.2 when the solvent used is tetrahydrofuran/1 *M* buffer solution (5:1) (buffer: KH_2PO_4/Na_2HPO_4, pH 4.5–6.0; or ammonium acetate, pH 7.2). The action of the buffer is not necessarily linked to its pH since the use of phosphate buffer pH >6.5 or dilute buffer solution do not lead to rapid cleavage.

The method could be extended to the cleavage of 2,2,2-trichloroethylcarbamates to amines (30 min, pH 4.2; 18 h, pH 5.5) and of aryl 2,2,2-trichloroethyl carbonates to phenols (4 h, pH 4.2), so that selective cleavage of 2,2,2-trichloroethyl esters in the presence of 2,2,2-trichloroethyl carbamates and carbonates, and selective cleavage of 2,2,2-trichloroethyl carbamates in the presence of 2,2,2-trichloroethyl carbonates is in principle possible.



$$R-\overset{O}{\overset{\|}{C}}-O-CH_2-CCl_3 \xrightarrow{Zn/THF/H_2O,\ pH\ 4.2-7.2} R-\overset{O}{\overset{\|}{C}}-OH$$

$$R-NH-\overset{O}{\overset{\|}{C}}-O-CH_2-CCl_3 \longrightarrow R-NH_2$$

$$Ar-O-\overset{O}{\overset{\|}{C}}-O-CH_2-CCl_3 \longrightarrow Ar-OH$$

The esters were prepared using boron trifluoride etherate[6] (Method A) or refluxing toluene containing *p*-toluenesulfonic acid[7] (Method B), and the carbamate and carbonate according to literature procedures[5]. Yields refer to distilled or crystallized compounds and are not optimized.

The reaction was carried out on a 0.1–3.5 mmol scale, using the same proportion as indicated in the typical procedure given for hippuric acid. The examples listed in the Table serve to illustrate some application of the method.

The unmasked products were characterized by I.R., T.L.C., m.p., and mixture m.p.

We also found that the 2-iodoethyl ester[12] of hippuric acid is cleaved under the same conditions. Presumably, 2-iodoethyl carbamates[13] can be comparably cleaved, although this has not been demonstrated. No further work is planned in this area.

Regeneration of Hippuric Acid from its 2,2,2-Trichloroethyl Ester: Zinc dust[8] (2 g), followed by 1 *M* aqueous potassium dihydrogen phosphate (2 ml) are added to a rapidly stirred solution of hippuric acid 2,2,2-trichloroethyl ester[10] (1.0 g) in tetrahydrofuran (10 ml) at room temperature. The resultant slurry[9] is stirred for 10 min; during this time a slight temperature increase to 28° is noticed. Zinc is filtered off, the filtrate is stirred with an ion-exchange resin (Fisher Rexyn 101-H), filtered, and concentrated. The residue is crystallized from methanol/ether; yield: 440 mg (76%).

We wish to thank the National Research Council of Canada for financial support.

Received: February 9, 1976

---

[1] R. B. Woodward, et al., *J. Am. Chem. Soc.* **88**, 852 (1966).

[2] R. B. Woodward, *Science* **153**, 487 (1966).

[3] I. G. Wright, et al., *J. Med. Chem.* **14**, 420 (1971).

[4] F. Eckstein, *Angew. Chem.* **77**, 912 (1965); *Angew. Chem., Int. Ed. Engl.* **4**, 876 (1965).

[5] T. Windholz, D. Johnston, *Tetrahedron Lett.* **1967**, 2555.

[6] P. K. Kadaba, *Synthesis* **1971**, 316.

[7] D. Swern, E. Jordan, *J. Am. Chem. Soc.* **67**, 902 (1945).

[8] Zinc dust was untreated and purchased from Anachemia Chemicals Ltd., Montreal, Canada, or Fisher Scientific.

[9] In preliminary experiments, we found that the ratio THF/salt-solution is very critical, after initial stirring a slurry should result. (No cleavage is observed when two layers are present).

[10] Bong Young Chung, *Ph. D. Thesis*, McGill University, Montreal, 1975.

[11] M. Bachi, *Synthesis of β-lactum structures related to penicillin*, in: *5th Intern. Conf. of Heterocyclic Chem., University of Bratislava, July 13–18 (1975). Abstr. of papers sec. 1, p. 23.*

[12] J. Grimshaw, *J. Chem. Soc.* **1965**, 7136.