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Reductive Cleavage of TROC Groups Under Neutral Conditions with Cadmium-Lead Couple

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ABSTRACT: Cadmium-lead couple induces rapid and efficient reductive cleavage of TROC groups under extremely mild conditions. The couple is readily prepared and it is not pyrophoric.

2,2,2-Trichloroethyl carbamates, carbonates, and esters are exceedingly useful protecting group for amines, alcohols and carboxylic acids, respectively.² These groups are conveniently cleaved under reductive conditions, e.g., with Zn/AcOH³, Zn and mildly acidic buffers⁴, Co phthalocyanine anion⁵, selenide⁶ or telluride⁷ reagents; or by electrochemical procedures.⁸ In connection with ongoing synthetic work, we required a reductive deblocking technique that would work well at pH 7 and that would not harm a sensitive dibromodienone unit present in certain intermediates of ours. Known procedures reasonably conforming to our boundary conditions proved to be unsatisfactory. First, reaction rates were extremely slow at neutral pH, even with Zn/Cu couple. Furthermore, various permutations of the following problems were observed, depending on precise conditions: stalling of the reaction; mono-dechlorination of the trichloroethyl group without cleavage; dehalogenation of the dibromodienone; dienone-phenol rearrangement. Two reports have addressed the advantages of Zn/Pb couple⁹ and Cd/AcOH¹⁰ for these reductive deprotections. Major improvements were realized in our systems by the use of these excellent methods; however, a truly superior deblocking reagent emerged in the form of 10% Cd/Pb couple. This readily prepared substance cleaves trichloroethyl groups rapidly (30-45 min) and efficiently (90-95 %) under extremely mild conditions (pH 7, 1M aq. NH₄OAc buffer). Five equivalents of Cd per trichloroethyl group are optimal. Representative experiments are summarized in Table 1 (TROC = trichloroethoxy carbonyl; TCE = trichloroethyl), and typical procedures are as follows.¹¹

<u>Preparation of 10 % Cd/Pb couple</u>. Yellow lead oxide, (litharge, PbO, 108 mg, 0.49 mmol), was dissolved in 5 ml of warm 50 % aq. AcOH, and the solution was slowly added to a vigorously stirred suspension of Cd dust (Aldrich, 100 mesh, 546 mg, 4.9 mmol) in deionized water (10 ml). The Cd darkened as Pb deposited on its surface, and formed clumps that were gently broken up with a glass rod. The dark, non-pyrophoric Cd/Pb couple was filtered, washed with water, then acetone, vacuum dried, crushed (glass rod), and stored in a closed vessel.

<u>Trichloroethyl carbamate cleavage</u>. 10 % Cd-Pb couple (5 mmol of Cd) was added to a rapidly stirring mixture of N-TROC-tetrahydroquinoline (1 mmol), THF (4 ml) and aq. 1 N NH₄OAc (4 ml). Cloudiness developed, and when the reaction completed (TLC, 45 min) the solids were filtered and rinsed with water and with ether. The filtrate was basified (aq. NaOH) and the product was extracted with ether (92 % yield).

<u>Trichloroethyl ester cleavage</u>. The above procedure was applied to 2,2,2-trichloroethyl (TCE) cinnamate, except that the aqueous/ether mixture was *acidified* (aq. HCl) prior to ether extraction (93 % yield).

<u>Trichloroethyl carbonate cleavage</u>. The above procedure was applied to cholesteryl 2,2,2-trichloroethyl carbonate, except that the aqueous/ether mixture was directly extracted with ether (94 % yield).



Table 1: Representative examples of the new deblocking procedure

^a Crude yield of essentially pure material; ^bminutes

The new procedure is better than other methods¹² for deprotection of N-TROC indole (Table). Esters are deprotected much faster than carbamates / carbonates. Unactivated halogens, even iodide, and dibromodienones, e.g., 1, survive unscathed, but nitro and azido groups do interfere. At pH 7, azide reduction proceeds normally to the amine, but a nitro group yields a mixture of products. However nitro group reduction to the amine occurs cleanly in the presence of AcOH, and it may be effected simultaneously to TROC removal, e. g. $2 \rightarrow 3$ (Eq. 1).



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- 11. CAUTION: Cd, Pb, and their compounds are toxic and probably carcinogenic, and Cd dust is especially hazardous. Appropriate safety precautions must be taken during handling and disposal of these substances.
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