Tetrachlorophthaloyl as a Versatile Amine Protecting Group

John S. Debenham and Bert Fraser-Reid*

Paul M. Gross Chemical Laboratory, Department of Chemistry, Duke University, Durham, North Carolina 27708

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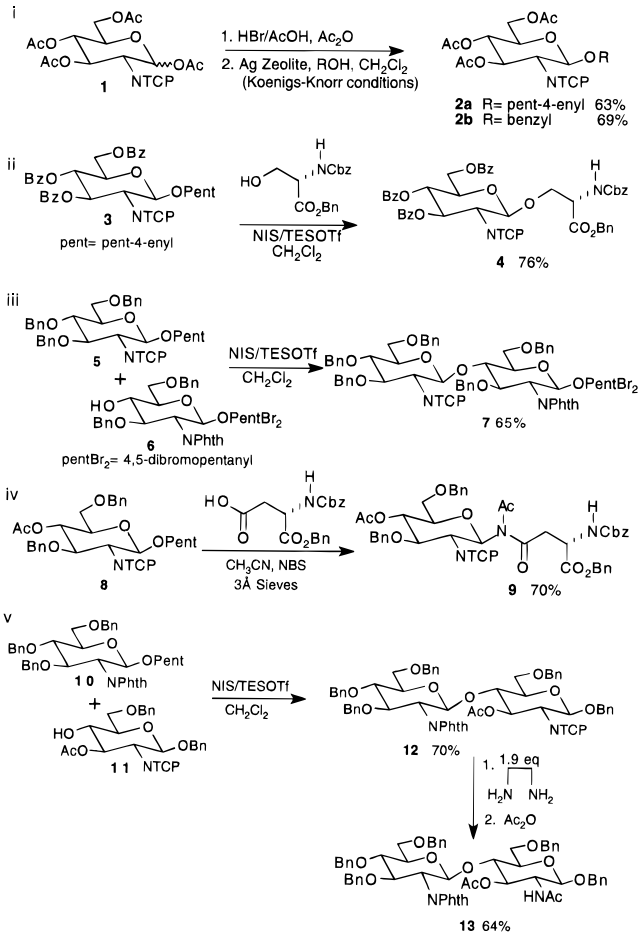
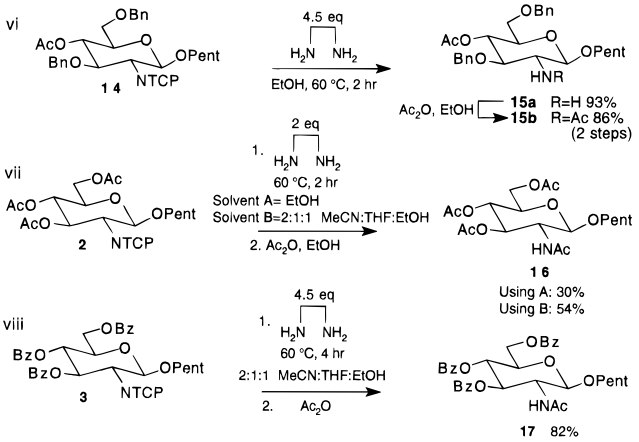
We reported recently that the pent-4-enoyl and tetrachlorophthaloyl (TCP)[1] groups serve as protecting devices for amine functionalities that can be removed orthogonally and chemoselectively.[2] TCP belongs to the class of cyclic imidic protecting groups including the parent phthaloyl,[3] maloyl,[4] and dithiosuccinoyl[5] that have served synthetic organic chemists well,[6] and hence, we have invested additional effort in examining its potential. In this paper, we report that the TCP group offers a wealth of advantages in synthetic manipulations where a primary amine must be carried in protected form. *Of special importance is the survival of carboxylate esters during TCP cleavage.* Our examples are chosen mainly from the carbohydrate domain in view of the current high interest in glycoproteins[7] and amino glycans.[8]

The TCP group has been found to be stable to a wide range of reagents normally used in standard oligosaccharide transformations (*vide infra*)[2,9] which therefore makes it possible to install this inexpensive protecting device at the outset of a major synthesis with confidence about its survival prospects.[10] That TCP is able to exercise neighboring group participation in spite of being deactivated is demonstrated in eqs i−iii, and the procedure for direct N-linkage of amino acid residues developed in our laboratory[11] is effectively applied to **8**, leading to high yields of **9** as a single diastereomer (eq iv). Thus, Phth and TCP are comparable from the standpoints of ease of installation[3a] and stereodirecting properties. Furthermore, there is no substantial reactivity difference between these protected donors when NIS/TESOTf[12] is used as promoter, as both react to completion within minutes.



It is with respect to the conditions for its removal that the attractiveness of the TCP group is accentuated. Hindsgaul and co-workers have shown that cleavage of the parent phthalimide function can be achieved with ethylenediamine.[13] However, the reagent must be used literally as cosolvent at temperatures of 80−100 °C up to 20 h, conditions so harsh that amino acids may be racemized and other base sensitive functionalities affected.



We have found that the TCP group can be removed with as little as 1.5 equiv of ethylenediamine for sensitive substrates. However, in most cases, 2−4 equiv can be

(1) The use of TCP group for amine protection in oligosaccharide synthesis was first reported (J. S. Debenham and B. Fraser-Reid) at the XVIIth International Carbohydrate Symposium, Ottawa, Canada, July 1994, paper B1.38, and subsequently (J. S. Debenham and B. Fraser-Reid) at the 209th National Meeting of the American Chemical Society, Anaheim, CA, April 1995, paper CARB 008.

(2) Debenham, J. S.; Madsen, R.; Roberts, C.; Fraser-Reid, B. *J. Am. Chem. Soc.,* **1995**, *117*, 3302−3303.

(3) (a) Lemieux, R.; Takeda, T.; Chung, B. In *Synthetic Methods for Carbohydrates*; El Khadem, H. S., Ed.; ACS Symposium Series: Washington, DC, 1976; Vol. 39, pp 90−115. (b) Ing, H.; Manske, R. *J. Chem. Soc.* **1926**, 2348−2351.

(4) Zehavi, U. *J. Org. Chem.* **1977**, *42*, 2819−2821.

(5) (a) Barney, G.; Merrifield, R. B. *J. Am. Chem. Soc.* **1977**, *99*, 7363−7365. (b) Meinjohanns, E.; Meldal, M.; Paulsen, H.; Bock, K. *J. Chem. Soc., Perkin Trans. 1* **1995**, 405−415.

(6) For example; see the chapters on protection of amino groups in the most extensive of two recent source books: (a) *Protecting Groups*; Kocienski, P. J., Ed.; Thieme:Stuttgart, 1994; Chapter 6. (b) *Protecting Groups in Organic Synthesis*, 2nd ed.; Greene, T. W., Wuts, P. G. M., Eds.; John Wiley & Sons, Inc.: New York, 1991; Chapter 7.

(7) Garg, H. G.; von dem Bruch, K.; Kunz, H. *Advances in Carbohydrate Chemistry and Biochemistry*; Horton, D., Ed.; Academic Press, Inc.: San Diego, 1994; Vol. 50, pp 277−310.

(8) Kjellén, L.; Lindahl, U., *Annu. Rev. Biochem.* **1991**, *60*, 443−475. Hassell, John R.; Kimura, James H; Hascall, Vincent C. *Annu. Rev. Biochem.* **1986**, *55*, 539−567.

(9) Castro-Palomino, J. C.; Schmidt, R. R. *Tetrahedron Lett.* **1995**, *36*, 5343−5346.

(10) TCP is the cheapest of a group of deactivated phthalides, including mononitro and mono- and dihalo. Additionally, many of the TCP derivatives that we have prepared tend to crystallize readily, the attendant advantages for large scale work being obvious.

(11) (a) Handlon, A. L.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1993**, *115*, 3796−3797. (b) Ratcliffe, A. J.; Konradson, P.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1990**, *112*, 5665−5666.

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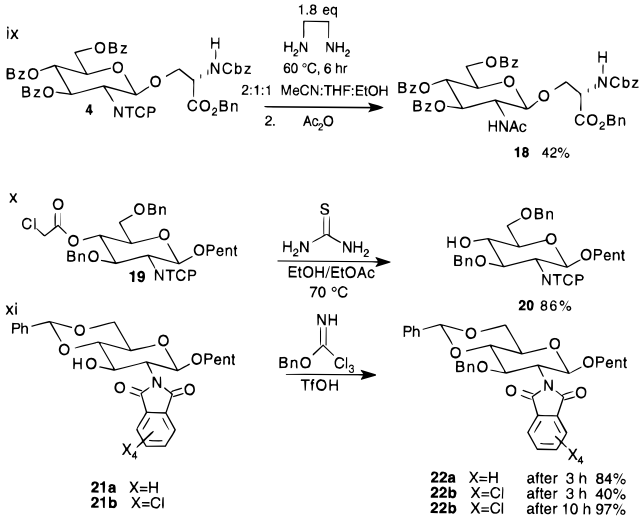
safely used, under which conditions cleavage is completed within reasonable periods of time. It is worth noting that the cleavage byproduct is insoluble in many commonly used solvents (CH_2Cl_2, DMF, DMSO, acetone, EtOAc, MeOH, etc.) and is therefore conveniently removed by filtration.[14]

The TCP group may also be placed on the acceptor molecule as illustrated with **11** (eq v) forming the differentially protected chitobiose derivative **12**. The latter compound has been used to demonstrate an advantage of TCP in the chemoselective cleavage leading to product **13** in 64% yield.

The survival of esters under the conditions for TCP cleavage was of primary interest to us. The C4-OAc group in **14** (eq vi) is hindered, and hence, its presence in product **15** might have been fortuitous. Indeed, when triacetate **2a** was treated under comparable conditions, product **16** (eq vii) was obtained in only 30% yield. An increase in yield to 54% was experienced with MeCN/THF/EtOH (2:1:1), indicating that a change in solvent can have a salutary effect. However, exploration of this promising possibility was rendered less urgent by the experiment in eq viii which showed that benzoate esters in **3** survived the cleavage conditions very well. Thus, the yield of 82% over two steps for **17** was most encouraging.

Reasons for our emphasis on ester survival are apparent in eq ix. With respect to the glycosyl serine **4** prepared in eq ii, treatment with ethylenediamine in a solvent of MeCN/THF/EtOH (2:1:1) followed by acetylation provided the N-acetylated glycopeptide **18** without racemization or transesterification. The importance of solvent should be noted, because when the reaction was carried out in the presence of MeOH complete transesterification and significant racemization were observed.



In cases where the synthetic plan requires that an ester be preserved, the susceptibility of the TCP group to bases as mild as ethylenediamine is advantageous. However, for the opposite selectivity, it is worthwhile to note that where ready removal of an ester is desired, chloroacetyl groups can be utilized. Thus, chloroacetyl esters can be removed efficiently with thiourea in the presence of a TCP group as exemplified in eq x.

In view of the importance of benzyl protecting groups in oligosaccharide synthesis, note should be taken of eq xi, which shows that acidic-benzylation[15] can be carried out on suitable TCP derivatives in quantitative yield.[16] However, as is obvious from eq xi, there may be a decrease in reactivity for TCP acceptors as compared to the Phth counterpart.[17]

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Supporting Information Available: Listings of experimental procedures for the preparation of all key compounds with selected analytical data (8 pages).

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(13) Kanie, O.; Crawley, S. C.; Palcic, M. M.; Hindsgaul, O. *Carbohydr. Res.* **1993**, *243*, 139−164.

(14) It is worth noting that the ethylenediamine-based cleavage product's lack of solubility makes it difficult to positively characterize.

(15) Wessel, H.-P.; Iverson, T; Bundle, D. R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2247−2250.

(16) It should be noted that the TCP group is unstable to the strongly basic conditions necessary for standard NaH/BnBr benzylations.

(17) Whether this reactivity difference can be leveraged into an armed/disarmed protocol for amino acceptors is currently being tested in our laboratories.