The Mitsunobu Reaction of Tetrachlorophthalimide

Zhaozhong J. Jia, Sandra Kelberlau, Lars Olsson, G. Anilkumar, Bert Fraser-Reid*

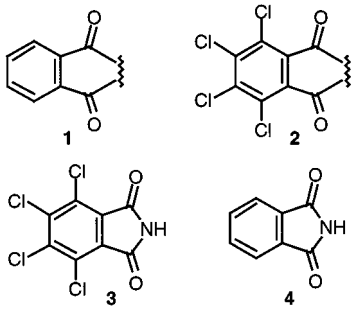
Natural Products and Glycotechnology Research Institute, Inc., 4118 Swarthmore Road, Durham, NC 27707, USA
Fax 919 493 6113; E-mail dglucose@aol.com

Received 9 March 1999

Abstract: Tetrachlorophthalimide is shown to be an excellent agent for Mitsunobu displacement of primary hydroxyl groups in a wide variety of substrates. Secondary alcohols also react readily, except in carbohydrate derivatives where there is a low rate of success. In a competition experiment between phthalimide and its tetrachloro counterpart, there was no trace of a product from the former.

Key words: Mitsunobu, tetrachlorophthalimide, hydroxyl displacement

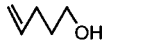
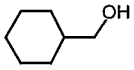
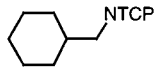
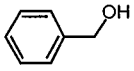
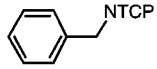
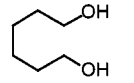
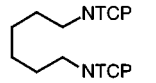
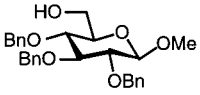
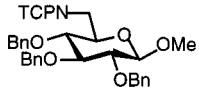
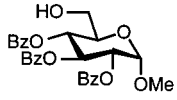
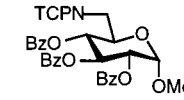
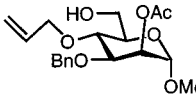
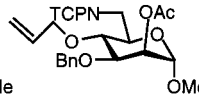
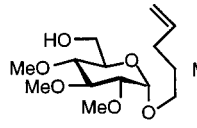
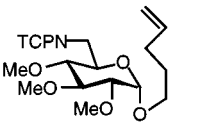
Mitsunobu reactions have emerged as common synthetic methods for substitution of hydroxyl groups by both intermolecular and intramolecular displacement.[1] Thus cyclic imides have been widely used for introducing amino functionalities.[2] In this connection, the phthaloyl group **1** is of interest since it is also widely used for nitrogen protection in organic syntheses.[3] However to avoid the harsh procedure needed for phthalimide deprotection, our group has been interested in use of the tetrachloro analog (TCP) **2** for nitrogen protection.[4] Mild cleavage of TCP is possible[5] in the presence of acetate, benzoate and unsubstituted phthalimide, as demonstrated in the synthesis of nodulation factor NodRf-III (C18:1, MeFuc).[6]



The four electron-withdrawing chlorine atoms on the aromatic ring not only faciliate nucleophilic attack at the imide carbonyls, but should also enhance the acidity of the imidic hydrogen. Thus tetrachlorophthalimide (TCP-NH) **3** should be more effective than unsubstituted phthalimide (Pht-NH) **4** in Mitsunobu reactions. In this manuscript we report our work on this problem.

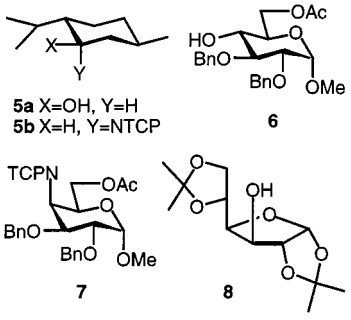
The Mitsunobu reactions with TCP-NH were studied by the following general procedure: To the mixture of alcohol, triphenylphosphine (TPP, 1.3 eq) and TCP-NH (1.3 eq) was added anhydrous THF (0.1-0.2 M). The mixture, usually a white slurry, was stirred vigorously under argon at room temperature. Diethyl azodicarboxylate (DEAD, 1.3 eq) was added by syringe, and the reaction mixture, usually a yellow clear solution, was stirred overnight. THF was then removed in vacuo. The residue was dissolved in $CHCl_3$ or CH_2Cl_2 and washed with water. Purification of the organic residue by column chromatography was readily monitored by UV visualization.

Table 1. Tetrachlorophthalimide Mitsunobu Reactions of Primary Alcohols

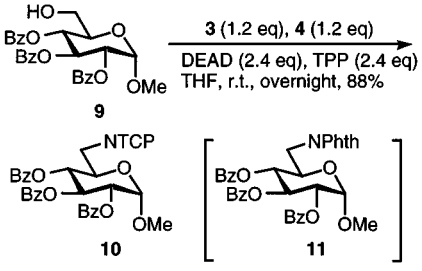
Entry	Precursor	Product	Yield
1			72%
2			84%
3			73%
4			78%
5			89%
6			90%
7			81%
8			55%

The results for a variety of primary alcohols are shown in Table 1. For simple primary alcohols (entries 1-4), the yields are uniformly over 70%. The procedure also works well to convert carbohydrate primary alcohols into TCP-protected nitrogen functions (entries 5-8). The presence of benzyl, allyl, benzoate or acetate protecting groups does not compromise the outcome. The success of the n-pentenyl glucoside precursor (entry 8) allows the amino synthon to be incorporated into these novel glycosyl donors,[7] prior to coupling reactions.

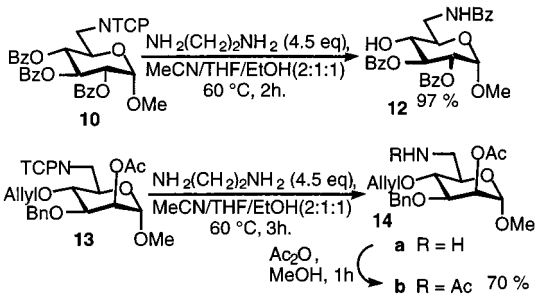
(-)-Menthol **5a** was chosen as a secondary alcohol and was found to react readily to give **5b** in 69% yield by the general procedure. However attempts with carbohydrate secondary alcohols were not encouraging. For precursor **6**, more than 90% starting material was recovered, after stirring for 95 hours at room temperature. Product **7** was obtained in only trace amounts. For precursor **8**, no reaction occurred at all after refluxing for over 100 hours. The failure for these two reactions could be reasoned by the difficulty for the bulky TCP-N nucleophile to approach the already sterically-hindered secondary alcohol and the difficulty for the sterically-hindered secondary alcohol to approach the activated triphenylphosphine to form the oxyphosphonium salt.



The Mitsunobu efficiency was assessed by allowing TCP-NH and Pht-NH to compete for sugar alcohol **9**. Thus 1 equivalent of **9**, 1.2 equivalents each of **3** and **4**, 2.4 equivalents each of DEAD and TPP were dissolved in THF and stirred at room temperature overnight. The isolated material was shown by ^{1}H and ^{13}C NMR to be exclusively **10**, with a 88% isolated yield. Compound **11**, synthesized independently, was not detected. This excellent Mitsunobu selectivity can be reasoned by the more acidic proton in **3**.



The merits of the process can be seen by the ease of deprotection. Thus treatment of **10** with 4.5 equivalents of ethylenediamine in MeCN/THF/EtOH (2:1:1) at 60 °C was complete after 2 hours. The product obtained in 97% yield was the benzamide **12,** identifiable by its mass spectrum (FAB 505.2 M^{+}), and its failure to react with acetic anhydride in methanol. In the case of **13** (see Table 1, entry 7), comparable deprotection gave amine **14a,** survival of the C2-OAc group being evident from the NMR spectrum. Acetylation in methanol then gave the acetamide **14b** in 70% overall yield from **13.**



In conclusion, tetrachlorophthalimide has been successfully employed in Mitsunobu reactions to convert a free hydroxyl into a delicately tetrachlorophthalimido protected nitrogen function. This reaction provides new possibilities in organic synthesis for nitrogen introduction, and nitrogen protection-deprotection manipulations.

Acknowledgement

We gratefully acknowledge support by the National Institutes of Health (GM 40171) and Insmed Pharmaceuticals, Inc., Richmond, Virginia, USA.

References and Notes

(1) For reviews, see: (a) Hughes, D. L., *Org. React.* **1992**, *42*, 335; (b) Castro, B.R., *Org. React.* **1983**, *29*, 1; (c) Mitsunobu, O., *Synthesis* **1981**, 1.
(2) For recent applications, see: (a) Ong, C. W.; Wang, H. M.; Chang, Y. A., *J. Org. Chem.* **1996**, *61*, 3996; (b) Cherney, R. J.; Wang, L., *J. Org. Chem.* **1996**, *61*, 2544; (c) Walker, M. A., *J. Org. Chem.* **1995**, *60*, 5352; (d) Brown, F. K.; Brown, P. J.; Bickett, D. M.; et al., *J. Med. Chem.* **1994**, *37*, 674.
(3) (a) Kocienski, P. J., *Protecting Groups*; Georg Thieme Verlag: Stuttgart, 1994. (b) Lemieux, R. U.; Takeda, T.; Chung, B. Y., *Synthetic Methods for Carbohydrates*; El Khadem, H. S., Ed.; ACS Symposium Series, Washington, D.C., 1976; vol. 39, p. 90.
(4) (a) Debenham, J. S.; Madsen, R.; Roberts, C.; Fraser-Reid, B., *J. Am. Chem. Soc.* **1995**, *117*, 3302; b) Debenham, J. S.; Fraser-Reid, B., *J. Org. Chem.* **1996**, *61*, 432; (c) Debenham, J. S.; Debenham, S. D.; Fraser-Reid, B., *Bioorg. Med. Chem.* **1996**, *4*, 1909.
(5) Debenham, J. S.; Rodebaugh, R.; Fraser-Reid, B., *Liebigs Ann./Recueil* **1997**, 791.
(6) (a) Debenham, J. S.; Rodebaugh, R.; Fraser-Reid, B., *J. Org. Chem.* **1996**, *61*, 6478; (b) Debenham, J. S.; Rodebaugh, R.; Fraser-Reid, B., *J. Org. Chem.* **1997**, *62*, 4591.
(7) (a) Fraser-Reid, B.; Udodong, U. E.; Wu, Z.; Ottosson, J. R.; Merritt, J. R.; Rao, C. S.; Roberts, C.; Madsen, R., *Synlett* **1992**, 927; (b) Fraser-Reid, B.; Madsen, R., *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker, Inc.: New York, 1997; Chap. 14, p. 339.

Article Identifier:
1437-2096,E;1999,0,05,0565,0566,ftx,en;S07698ST.pdf