Two New Orthogonal Amine-Protecting Groups That Can Be Cleaved under Mild or Neutral Conditions[1,2]

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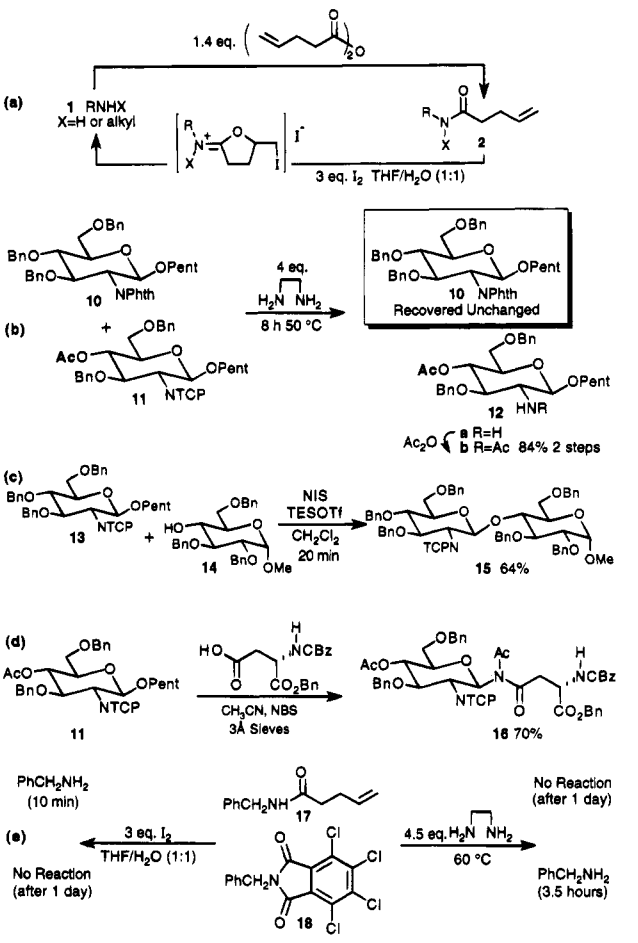
Amines are widespread among biologically important natural products that are the foci of extensive synthetic effort.[4] Because of their high reactivity, amines must usually be protected during synthetic operations,[5] the protecting group frequently serving the additional purpose of negating the amine's basicity, a task which can be efficiently accomplished by acylation. However, deprotection of the resulting amides or carbamates requires conditions that may be threatening to the natural product itself or functionalities thereon. This is particularly true with carbohydrates, where amino-deoxy modifications are ubiquitous among O- and N-linked glycoproteins,[6] and where the presence of variously differentiated *N*-acyl residues poses severe logistical problems for synthesis. The ability to remove and/or exchange amino-protecting groups readily and chemospecifically under mild conditions would be advantageous for syntheses of various natural products. Our successes with *n*-pentenyl-based hydroxyl-protecting groups[7] encouraged us to turn our attention to amines. In this paper we introduce two such candidates, the pent-4-enoyl and tetrachlorophthaloyl (TCP) groups, which can be removed chemoselectively under neutral or mild conditions and, in addition, are uniquely orthogonal[8] to each other.

The requirement to reduce basicity mandated *N*-pent-4-enoylation.[9] Installing the protecting group by the use of pent-4-enoic anhydride,[10] e.g., **1** → **2** (Scheme 1a), was uneventful and usually proceeded in virtually quantitative yield.[11] However, deprotection, e.g., **2** → **1**, required considerable experimentation[12] to develop the best conditions of solvent and reagents, as well as the nature and quantity of the electrophile.

Scheme 1



Eventually the use of 3 equiv of iodine in 1:1 THF/H_2O was found to serve most needs.[13] From the sample of test cases in Figure 1 it is seen that deprotection of both primary and secondary amines occurs rapidly, selectively, and efficiently under neutral conditions.

In view of the oxidative nature of the medium, deprotection of the methionine derivative, **4b** → **4a** (Figure 1), was a testament to the mildness of the reaction conditions as, to a lesser extent, was deprotection of the *p*-methoxybenzyl glycoside, **5a** → **5b**. Of particular interest was the window of chemoselectivity manifested by the survival of the glycosidic *O*-pentenyl group during de-*N*-pent-4-enoylation, **6a** → **6b**. The latter result is undoubtedly due to the high electron density on the amide oxygen of **6a**, which facilitates formation of the imidylium ion intermediate (see Scheme 1a).

A problem with 2-*N*-acyl-2-deoxyglycosyl donors is that neighboring group participation during attempts at glycosidation invariably leads to oxazolines.[14] However, this did not affect coupling of **7** and **8** since a good yield of disaccharide **9a** was obtained. Unfortunately, when the glycosyl acceptor was a secondary alcohol, the results were not encouraging, in keeping with literature precedents for analogous 2-NH-Ac glycosyl donors.[14]

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(2) Patent pending for the methods described in this paper.
(3) (a) R.M. thanks the Danish Technical Research Council for a P. D. Fellowship. (b) C.R. is the recipient of a NIH Award for Under-represented Minorities.
(4) For numerous examples, see: Krohn, K.; Kirst, H. A.; Maag, H. *Antibiotics and Antiviral Compounds: Chemical Synthesis and Modification*; VCH: Weinheim, 1993.
(5) For example, see the chapters on protection of amino groups, the most extensive of two recent source books: (a) Kocienski, P. J. *Protecting Groups*; Thieme: Stuttgart, 1994; Chapter 6. (b) Greene, T. W.; Wuts, P. G. M. *Protecting Groups in Organic Synthesis*; 2nd ed.; John Wiley & Sons, Inc. New York, 1991; Chapter 7.
(6) 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.
(7) (a) Wu, Z.; Mootoo, D. R.; Fraser-Reid, B. *Tetrahedron Lett.* **1988**, *29*, 6549−6552. (b) Madsen, R.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1994**, 749−750.
(8) Barany, G.; Merrifield, R. B. *J. Am. Chem. Soc.* **1977**, *99*, 7363−7365.
(9) Lopez, J. C.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1991**, 159−161.
(10) Ellervik, U.; Magnusson, G. *Acta Chem. Scand.* **1993**, *47*, 826−828.
(11) Representative procedure: To an ice-cooled solution of L-methionine methyl ester hydrochloride (1.0 g, 5.01 mmol) and NEt_3 (1.39 mL, 10 mmol) in CH_2Cl_2 (6 mL) and MeOH (2.4 mL) was added pent-4-enoic anhydride (1.33 mL, 7.05 mmol). The reaction mixture was stirred at 0 °C for 20 min and then diluted with $CHCl_3$ (12 mL). The solution was washed with saturated aqueous $NaHCO_3$ (12 mL), dried, and concentrated. The residue was purified by flash chromatography (2:3 petroleum ether/EtOAc) to afford the amide, 1.12g (91%).
(12) Details of our efforts will be given in the full paper.
(13) Representative procedure: The pentenoyl amide (0.30 mmol) was dissolved in an organic solvent (1 mL), and an equal volume of H_2O (1 mL) was added subsequently, resulting in a cloudy suspension. Additional organic solvent was then added slowly until the turbid solution became clear. The reaction mixture was treated with I_2 (3 equiv) and stirred until completion. The reaction was quenched with ammonium thiosulfate and concentrated. The crude material was concentrated *in vacuo* and then flash chromatographed directly to produce the desired amine.
(14) See, for example: (a) Bochkov, A. F.; Zaikov, G. E. *Chemistry of the O-Glycosidic Bond*; Pergamon Press: Oxford, 1979; Chapter 2. (b) Banoub, J.; Boullanger, P.; Lafont, D. *Chem. Rev.* **1992**, *92*, 1167−1195.

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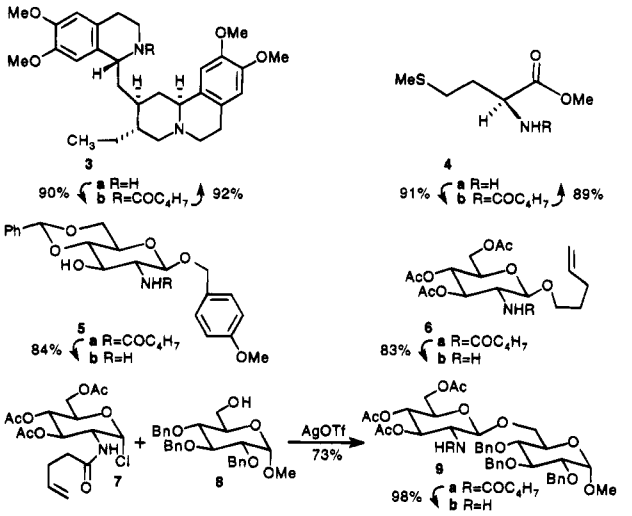

Figure 1. Pent-4-enoylation/de-pent-4-enoylation of amides. For conditions, see footnotes 11 and 13.

The classical solution to this dilemma resorts to phthaloyl protecting groups,[15] but their removal is often quite difficult.[16] Although various solutions have been proposed, the reagents and/or reaction conditions are not sufficiently chemospecific for application to complex glycoprotein synthesis.[17]

We reasoned that electron-withdrawing groups should facilitate phthalimido cleavage. 4-Nitrophthalimides[18] and 3,4,5,6-tetrachlorophthalimides (TCP) were examined, but results with the former were not generally encouraging. Furthermore, the fact that 100 g of 4-nitrophthalic anhydride costs $370, as against $12 for the tetrachloride analog, adds to the attractiveness of the latter.

Exploratory experiments showed that the TCP group[19] could be cleaved rapidly and cleanly by use of a slight excess of ethylenediamine in ethanol.[17b] The contrast with the phthalimide counterpart is succinctly conveyed in Scheme 1b. Thus when equimolar amounts of glucosamine derivatives **10** and **11** were made to compete for 4.5 equiv of ethylenediamine, the unsubstituted phthalimide was recovered, while the tetrachloro analog suffered cleavage to give glucosaminide **12a**. *Of special significance is the survival of the C4-OAc in* ***12a****, a powerful demonstration of the mildness of the cleavage conditions.*

However, it should be emphasized that withdrawal of electron density does not inhibit neighboring group participation, a crucial requirement for synthesis of β-glycosidic linkages. Thus, the β-(1→4) linked disaccharide **15** was obtained rapidly and efficiently. Similarly the β-N-linked glycopeptide **16** (Scheme 1d) was obtained using our recently published methodology.[20]

The fact that the pent-4-enoyl and TCP protecting groups can each be cleaved specifically suggests that it should be possible to use them orthogonally. This concept has been shown with the benzylamine derivatives **17** and **18** (Scheme 1e).

In conclusion, we have developed two new amine-protecting groups that can be installed using standard methods, each of which can be cleaved chemospecifically under mild conditions in the presence of the other. A further observation of considerable practical significance is that the pent-4-enoyl and TCP derivatives examined thus far are highly crystalline and readily precipitate out of solution after workup. Hence there is no need for purification by column chromatography. The implication for large-scale preparation is obvious. Experiments to exploit the versatility of these new protecting groups are underway and will be reported in due course.

Supplementary Material Available: Listings of experimental procedures for the preparation of all key compounds with selected analytical data (9 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(15) Lemieux, R.; Takeda, T.; Chung, B. In *Synthetic Methods for Carbohydrates*; El Khadem, H. S., Ed.; ACS Symposium Series 39; American Chemical Society: Washington, DC, 1976; pp 90−115.

(16) For examples, see: (a) Spijker, N. M.; Westerduin, P.; van Boeckel, C. A. A. *Tetrahedron* **1992**, *48*, 6297−6316. (b) Matsuzaki, Y.; Ito, Y.; Nakahara, Y.; Ogawa, T. *Tetrahedron Lett.* **1993**, *34*, 1061−1064. (c) Koeman, F. A. W.; Meissner, J. W. G.; van Ritter, H. R. P.; Kamerling, J. P.; Vliegenthart, J. F. G. *J. Carbohydr. Chem.* **1994**, *13*, 1−25.

(17) See, for example: (a) Ing, H.; Manske, R. *J. Chem. Soc.* **1926**, 2348−2351. (b) Kanie, O.; Crawley, S. C.; Palcic, M. M.; Hindsgaul, O. *Carbohydr. Res.* **1993**, *243*, 139−164. (c) Wolfe, S.; Hasan, S. K. *Can. J. Chem.* **1970**, *48*, 3572−3579. (d) Dasgupta, F.; Garegg, P. *J. Carbohydr. Chem.* **1988**, *7*, 701−707.

(18) While this work was in progress, Tsubouchi and co-workers have also demonstrated that nitro substitution at the 4-position of the phthalimido ring leaves benzylamine analogs more susceptible to cleavage using methylhydrazine. Tsubouchi, H.; Tsuji, K.; Ishikawa, H. *Synlett* **1994**, 63−64.

(19) Installed by the method of Lemieux. See ref 15.

(20) Handlon, A. L.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1993**, *115*, 3796−3797.