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(2-Nitrophenyl)acetyl: A New, Selectively Removable Hydroxyl Protecting Group

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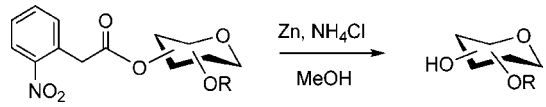
ABSTRACT



The utility of the (2-nitrophenyl)acetyl (NPAc) group for the protection of hydroxyl functions is reported. (2-Nitrophenyl)acetates are readily prepared starting from the commercially available, inexpensive (2-nitrophenyl)acetic acid, and these esters are stable under a series of common carbohydrate transformations. The NPAc group can be removed selectively using Zn and NH_4Cl without affecting a series of common protecting groups. This new protecting group is orthogonal with the commonly used *tert*-butyldimethylsilyl, levulinoyl, 9-fluorenylmethoxycarbonyl, naphthylmethyl, and *p*-methoxybenzyl groups.

The chemistry of multifunctional organic compounds relies heavily on extensive use of protecting groups. The protecting groups should be easily introduced using readily available, inexpensive chemicals, they should be stable to a wide range of reaction conditions, as well as during workup and purification, and, additionally, they should be removable selectively, under mild conditions without causing any other undesired chemical transformation. Although an enormous number of protecting groups are reported,[1] only a small set of these groups is used routinely, as many of the reported protecting groups only partly meet the above criteria. The concept of orthogonal protection,[2] in which any of a set of different protecting groups can be removed selectively without affecting the others, is particularly attractive in the carbohydrate field, as a strategy leading to "standardized intermediates"[3] for oligosaccharide synthesis. For hydroxyl groups, only a few sets of orthogonal protecting groups are reported, each consisting of only 2−3 individual groups.[4] There is still a continuous need for additional, new protecting groups in synthetic carbohydrate chemistry, in particular for protecting groups that are orthogonal to the commonly used ones.

Assisted cleavage is a very useful concept for developing new protecting groups. In assisted cleavage, the protecting groups have extra functionality and deprotection is initiated by chemical transformation of this auxiliary function. The modification of the auxiliary function results in a readily cleavable form or, frequently, in spontaneous deprotection. A variety of protecting groups have been introduced recently on the basis of this principle including, among others, the 4-acetoxy-2,2-dimethylbutyryl,[5] the 2-(chloroacetoxymethyl)benzoyl,[6] the 2-(chloroacetoxyethyl)benzoyl,[7] the 3-(2′-benzyloxyphenyl)-3,3-dimethylpropanoyl,[8] the 2-(allyloxy)phenylacetyl,[4d] and the 2-(prenyloxymethyl)benzoyl,[9] as well

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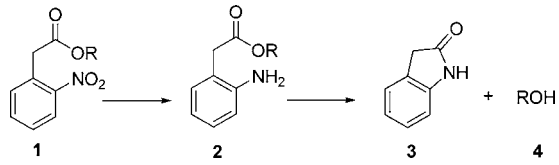
as the 4-azidobutyryl,[10] the 2-(azidomethyl)benzoyl,[11] and the 2-(azidomethyl)phenylacetyl[12] groups. Despite some of the attractive features of these protecting groups, they contain functional groups such as acetyl, chloroacetyl, benzyl, allyl, prenyl, and azido, which are used themselves as protecting or masking groups. This prevents selective deprotection of these groups in the presence of the above functionalities. The nitro group seems to be a more attractive auxiliary group for this purpose,[13] as it eliminates the above problems, and as a very large number of methods are known for its reduction to the highly nucleophilic amino group,[14] which then assists in the cleavage of the protecting group. In addition, a number of nitro compounds are available commercially, providing readily available starting materials for protecting groups. Thus, (2-nitrophenyl)acetic acid is an inexpensive, commercially available compound, and reduction of (2-nitrophenyl)acetates (**1**) leads to esters of (2-aminophenyl)acetic acid (**2**). Cyclization of **2** to the indolinone **3** is known to occur readily in a fast process releasing the corresponding alcohol (**4**) (Scheme 1).[15]

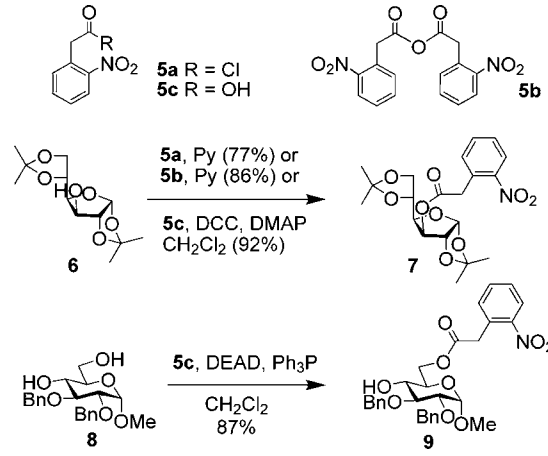
Scheme 1. Reductive Deprotection of (2-Nitrophenyl)acetates



We now report the (2-nitrophenyl)acetyl (NPAc) as a new hydroxyl protecting group, which can be removed selectively via assisted cleavage after reduction of the nitro group to an amine.

Introduction of the (2-nitrophenyl)acetyl group to different carbohydrate derivatives was readily accomplished by conventional methods, using the acid chloride[16] (**5a**), the previously unreported crystalline anhydride (**5b**), or the acid (**5c**) itself in carbodiimide-promoted acylations (Scheme 2).

Scheme 2. Introduction of the (2-Nitrophenyl)acetyl Group

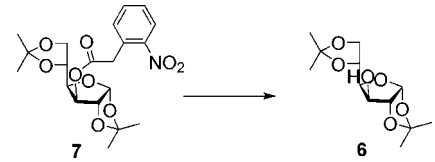


Alternatively, the Mitsunobu reaction was also used with the free acid, and it showed a remarkable regioselectivity toward the primary hydroxyl. In each case, the corresponding esters (**7**, **9**) were isolated in almost quantitative yields.

The (2-nitrophenyl)acetyl group was found to be stable under a series of common carbohydrate transformations, including acylations, acetalations, reductive acetal openings (BH_3·THF-TMSOTf),[17] and glycosylations.[18]

Different reductive conditions were investigated and found to be applicable to the removal of the (2-nitrophenyl)acetyl group (Table 1).

Table 1. Reductive Removal of the NPAc Protecting Group of **7**



entry	cleavage conditions	reaction time (h)	yield (%)
1	H_2, Pd/C, EtOH, rt	1	31
2	Zn, NH_4Cl, MeOH, rt	2	93
3	NH_4Cl, MeOH, rt	168	–
4	Zn, MeOH, rt	168	50
5	In, NH_4Cl, MeOH, rt	24	82
6	Al, NH_4Cl, MeOH, rt	120	75

Catalytic hydrogenation using palladium on carbon proceeded readily, the reaction mixture, however, contained, in

(9) Vatele, J.-M. *Tetrahedron Lett.* **2005**, *46*, 2299–2301.

(10) (a) Kusumoto, S.; Sakai, K.; Shiba, T. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1296–1298. (b) Velarde, S.; Urbina, J.; Pena, M. R. *J. Org. Chem.* **1996**, *61*, 9541–9545.

(11) (a) Wada, T.; Ohkubo, A.; Mochizuki, A.; Sekine, M. *Tetrahedron Lett.* **2001**, *42*, 1069–1072. (b) Love, K. R.; Andrade, R. B.; Seeberger, P. H. *J. Org. Chem.* **2001**, *66*, 8165–8176.

(12) Xu, J.; Guo, Z. *Carbohydr. Res.* **2002**, *337*, 87–91.

(13) Some of the previously reported protecting groups having a nitro auxiliary function, involve (a) the 4-methyl-4-nitropentanoyl group for hydroxyl and amine protection, see: Ho, T.-L. *Synth. Commun.* **1980**, *10*, 469–472. (b) the 2,2-dimethyl-2-(*o*-nitrophenyl)acetyl group for amine protection, see: Jiang, Y. Y.; Zhao, J.; Hu, L. Q. *Tetrahedron Lett.* **2002**, *43*, 4589–4592. (c) the 3-(4-*tert*-butyl-2,6-dinitrophenyl)-2,2-dimethylpropionyl group for amine protection, see: Johnson, F.; Habus, I.; Gentles, R. G.; Shibutani, S.; Lee, H. C.; Iden, C. R.; Rieger, R. *J. Am. Chem. Soc.* **1992**, *114*, 4923–4924. For the use of related groups in prodrug activation by bioreduction, see: (d) Hu, L. Q.; Liu, B.; Hacking, D. R. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 797–800. (e) Liu, B.; Hu, L. Q. *Bioorg. Med. Chem.* **2003**, *11*, 3889–3899.

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(15) For reaction kinetics data and mechanistic details on the cyclization of (2-nitrophenyl)acetates and propionates, see: (a) Fife, T. H.; Duddy, N. W. *J. Am. Chem. Soc.* **1983**, *105*, 74–79. (b) Kirby, A. J.; Mujahid, T. G.; Camilleri, P. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1610–1616.

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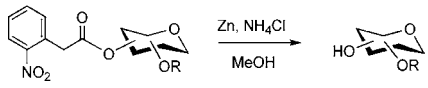
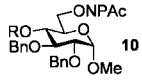
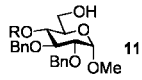
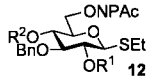
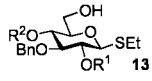
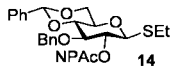
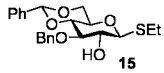
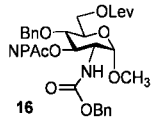
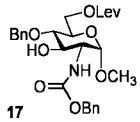
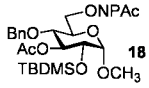
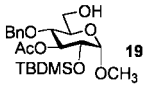
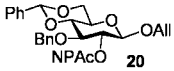
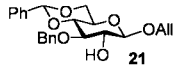
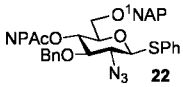
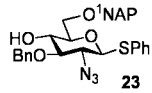
addition to **6**, its (2-aminophenyl)acetyl derivative, which could be converted to **6** by heating in ethanol. In contrast to the above two-stage removal of the NPAc group, deprotection using Zn and NH_4Cl could be accomplished in one step, the (2-aminophenyl)acetyl derivative has not accumulated during the reaction.[19] The reaction with Zn alone was sluggish, and NH_4Cl alone failed to give any reaction. In combination with NH_4Cl, zinc could be replaced with other metals, such as In and Al to effect the same transformation.

From the reagent combinations tested, Zn-NH_4Cl was selected for further investigations and a series of hexopyranoside derivatives were reacted in MeOH (Table 2). In all cases, the reactions afforded the corresponding hydroxy products in high yields.

Table 2. Compatibility of NPAc Removal with Common Protecting Groups Using Zn and NH_4Cl



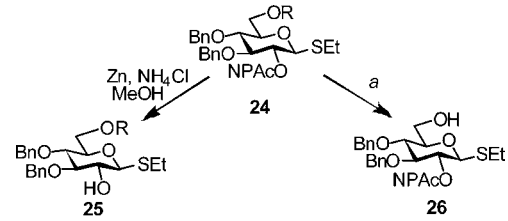
entry	substrate	product	yield (%)
1	 **10**	 **11**	
a	**10a** R = Bn	**11a** R = Bn	90
b	**10b** R = Bz	**11b** R = Bz	80
c	**10c** R = Ac	**11c** R = Ac	60[a]
2	 **12**	 **13**	
a	**12a** R^1 = Bz, R^2 = MPM	**13a** R^1 = Bz, R^2 = MPM	82
b	**12b** R^1 = Fmoc, R^2 = Bn	**13b** R^1 = Fmoc, R^2 = Bn	76
3	 **14**	 **15**	92
4	 **16**	 **17**	79
5	 **18**	 **19**	91
6	 **20**	 **21**	78
7	 **22**	 **23**	75

[a] In addition to **11c**, 22% of the acetyl migrated product, methyl 6-*O*-acetyl-2,3-di-*O*-benzyl-α-D-glucopyranoside, has also been isolated.

The reaction is compatible with most of the common protecting groups, such as benzyl (entries 1−7), 4-methoxybenzyl (entry 2a), allyl (entry 6), 1-naphthylmethyl (^{1}NAP) (entry 7), and *tert*-butyldimethylsilyl ethers (entry 5); benzylidene (entries 3 and 6) and isopropylidene (see Table 1) acetals, and acyl groups, including acetyl (entries 1c and 5), benzoyl (entries 1b and 2a), levulinoyl (entry 4), Fmoc (entry 2b), and benzyloxycarbonyl (entry 4) groups. Furthermore, the reactions could be performed on both *O*- and *S*-glycosides, and, importantly, the azido group also remained intact (entry 7).

The orthogonality of the (2-nitrophenyl)acetyl group against some of the common protecting groups was tested on compound **24** (Table 3).

Table 3. Orthogonality of the NPAc Group with Common Protecting Groups



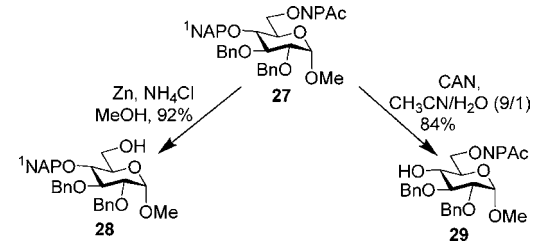
entry	substrate	product	yield (%)	*a*	yield of **26** (%)
1	**24a** R = TBDMS	**25a** R = TBDMS	81	Bu_4NF	78
2	**24b** R = Fmoc	**25b** R = Fmoc	73	Et_3N	81
3	**24c** R = Lev	**25c** R = Lev	78	H_2NNH_2	87
4	**24d** R = Bz	**25d** R = Bz	91	NaOMe	78

[a] Catalyst used.

Not only was the NPAc group selectively removed leaving the TBDMS, Fmoc and Lev groups intact, but any of these groups could also be cleaved with the appropriate reagents without affecting the (2-nitrophenyl)acetyl residue. In the case of compound **24** having the NPAc group at O-2, even selective removal of benzoyl group (entry 4) could be accomplished.[20]

Furthermore, the (2-nitrophenyl)acetyl group was also found to be orthogonal with the 1-naphthylmethyl group (Scheme 3).

Scheme 3. Orthogonality of the NPAc and ^{1}NAP Groups

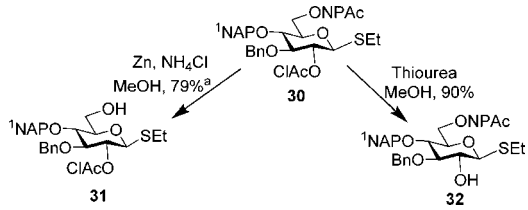


In case of the chloroacetyl group (Scheme 4), though selective removal of the ClAc group could be cleanly

(18) For examples of the above transformations in the presence of the NPAc group see the Supporting Information.

accomplished, removal of the NPAc group was accompanied by partial loss of the chloroacetyl group.

Scheme 4. Selective Removal of the NPAc and ClAc Groups



[a] In addition to **31**, 13% of the dechloroacetylated derivative of **31** was also isolated.

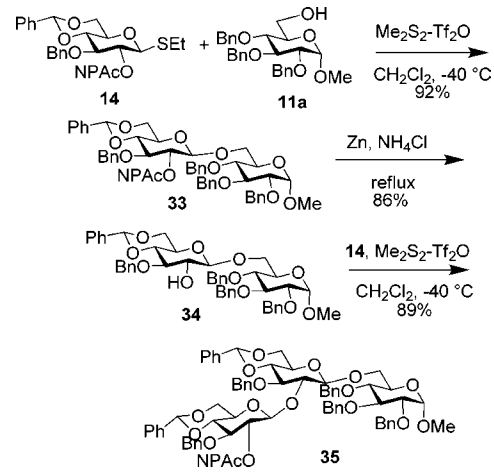
The utility of the (2-nitrophenyl)acetyl group for oligosaccharide synthesis is illustrated in Scheme 5.

Me_2S_2-Tf_2O-promoted glycosylation[21] of **11a** with the thioglycoside **14** afforded the β-(1→6)-linked disaccharide **33** in excellent yield. Selective removal of the NPAc group afforded the 2′-hydroxy derivative (**34**), further glycosylation of **34** with **14** gave the trisaccharide **35** suitable for further chain elongation.

The results indicate that the (2-nitrophenyl)acetyl group is an effective participating neighboring group, which leads to the selective formation of 1,2-*trans* glycosides in glycosylations.

In conclusion, we have introduced the (2-nitrophenyl)-acetyl group as a new, selectively removable hydroxyl protecting group. Preparation of NPAc esters can easily be performed by a variety of methods. The NPAc group is stable under most of the common carbohydrate transformations. It can be removed by different reductive methods. Selective removal of the NPAc group with Zn-NH_4Cl can be accomplished in the presence of the most common carbohydrate protecting groups. The NPAc group is orthogonal with TBDMS, Fmoc, Lev, NAP, and MPM protecting groups. Due to its advantegous properties, such as low cost, ease of introduction, selective removal, orthogonality with a series of common protecting groups, the (2-nitrophenyl)acetyl group is anticipated to become a valuable tool for the protection of hydroxyl groups.

Scheme 5. NPAc as a Participating Neighboring Group in Glycosylations



Acknowledgment. We are grateful to Dr. Pál Szabó (Chemical Research Center, Hungarian Academy of Sciences) and Dr. Izabella Lois (Chemical Research Center, Hungarian Academy of Sciences) for their assistance in recording the MS and NMR spectra, respectively. The skillful technical assistance of Ms. Katalin T. Palcsu (Chemical Research Center, Hungarian Academy of Sciences) is gratefully acknowledged.

Supporting Information Available: Experimental procedures, characterization data and copies of NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Interestingly, compound **3** could not be detected in deprotections of the NPAc group with Zn and NH_4Cl. We assume that a Zn complex of (2-aminophenyl)acetic acid is formed. For ready formation of Zn complexes of amino acids, see: Rombach, M.; Gelinsky, M.; Vahrenkamp, H. *Inorg. Chim. Acta* **2002**, *334*, 25–33, and references therein.

(20) Isolated acyl groups at O-2 of hexopyranosides are known to be relatively resistant to Zemplén deacylation. See: (a) Fügedi, P.; Lipták, A.; Nánási, P.; Szejtli, J. *Carbohydr. Res.* **1982**, *104*, 55–67. (b) Szurmai, Z.; Lipták, A.; Snatzke, G. *Carbohydr. Res.* **1990**, *200*, 201–208.

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