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A Tuneable Method for *N*-Debenzylation of Benzylamino Alcohols

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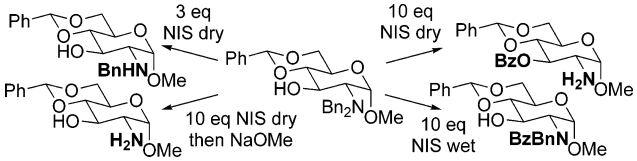
ABSTRACT



***N*-Iodosuccinimide provides a mild, convenient, and tuneable reagent for the selective mono- or didebenzylation in representative, multifunctionalized carbohydrate and amino acid derived *N*-dibenzylamines with neighboring *O*-functionality.**

The best-established method for the debenzylation of dibenzylamino groups involves hydrogenolysis over a heterogeneous palladium catalyst;[1] accompanying selectivity for mono- or di-*N*-debenzylation is rare. Incompatibility exists with other common hydrogenolyzable groups, particularly in sugars, such as Bn, Bz, or benzylidene. Davies et al. have described the monodebenzylation of differentially protected benzyl(*p*-nitrobenzyl)amines with ceric ammonium nitrate.[2] Debenzylation of benzylamines can also be achieved using other oxidizing agents.[3] However, a flexible homogeneous system with a wider range of potential outcomes starting from simple dibenzylamine substrates would be useful.

Access to differentially protected carbohydrate derivatives,[4] especially hexosamine derivatives,[5] is attractive because of their use in carbohydrate-scaffold libraries.[6] In particular the *N*-2 dibenzylamine substituent is a useful participatory *trans*-directing group in glycosyl donors.[7] Selective manipulations of complex hexosamine substrates such as **1** or **7** not only provide access to such systems but also provide a test of the compatibility of other protecting groups and functionality (e.g., benzylidene/methyl acetals, silyl ethers).[8]

In the course of our ongoing studies into the generation of imines through *N*-halogenation[9] we considered that sequential halogenation, elimination, and hydrolysis might provide a route to ready *N*-debenzylation. Initial studies revealed that although *N*-chlorosuccinimide was poorly effective, *N*-iodosuccinimide (NIS) could indeed effect debenzylation of dibenzylamines, and we show here its utility and selectivity in a variety of biomolecule component substrates, namely, carbohydrates and amino acids. Various

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(1) Greene, T. W.; Wuts, P. G. M. *Protecting Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999.

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(4) (a) Zhu, T.; Boons, G-J. *Tetrahedron: Asymmetry* **2000**, *11*, 199. (b) Prabhu, A.; Venot, A.; Boons, G.-J. *Org. Lett.* **2003**, 5, 4975. (c) Tanaka, H.; Amaya, T.; Takahashi, T. *Tetrahedron Lett.* **2003**, 44, 3053. (d) Peri, F.; Nicotra, F.; Leslie, C. P.; Micheli, F.; Seneci, P.; Marchioro, C. *J. Carbohydr. Chem.* **2003**, *22*, 57.

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(6) (a) Le, G. T.; Abbenante, G.; Becker, B.; Grathwohl, M.; Halliday, J.; Tometzki, G.; Zuegg, J.; Meutermans, W. *Drug Discovery Today* **2003**, *8*, 701. (b) Peri, F.; Cipolla, L.; Forni, E.; Nicotra, F. *Monatsh. Chem.* **2002**, *133*, 369. (c) Sofia, M. J.; Silva, D. J. *Curr. Opin. Drug Discovery Dev.* **1999**, *2*, 365. (d) Sofia, M. J.; Hunter. R.; Chan, T. Y.; Vaughan, A.; Dulina, R.; Wang, H.; Gange, D. *J. Org. Chem.* **1998**, *63*, 2802.

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(9) (a) Davis, B. G.; Maughan, M. A. T.; Chapman, T. M.; Villard, R.; Courtney, S. *Org. Lett.* **2002**, *4*, 103. (b) Chapman, T. M.; Courtney, S.; Hay, P.; Davis, B. G. *Chem. Eur. J.* **2003**, *9*, 3397. (c) Maughan, M. A. T.; Davies, I. G.; Claridge, T. D. W.; Courtney, S.; Hay, P.; Davis, B. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 3788.

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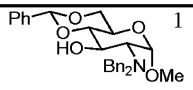
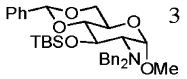
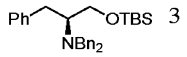
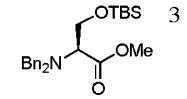
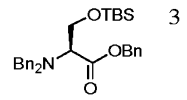
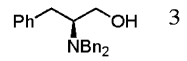
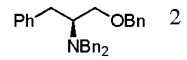
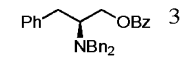
parameters were investigated: (a) equivalents of NIS, (b) Lewis acid additives, (c) base additives, (d) the role of water, and (e) reaction time (Table 1 and SI (p 36) for entries) to reveal a convenient debenzylation system that allows tuneable levels of deprotection (Scheme 1).

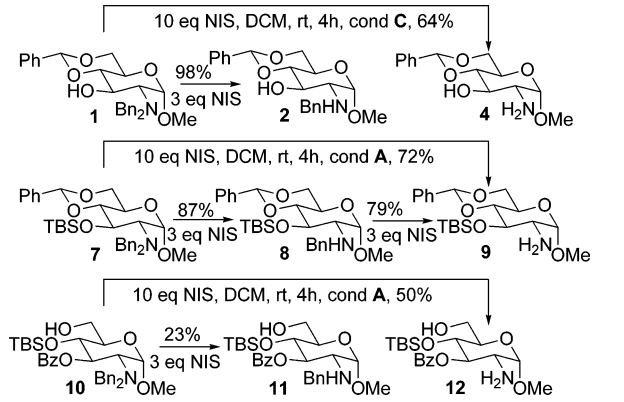
Table 1. Debenzylations with NIS

	R-NBn$_2$	Eq	[a]	h	Yield (%)[b] -NHBn	-NH$_2$	-NBnBz	Other
1	 **1**	1	**A**	96	50 (100)			50 **1**
7			**A**	4	50			50 **3**
18	 **7**	3	**A**	4	87	-	-	-
21	**7**	5	**B**	2	-	87	-	-
26	 **2 0**	3	**A**	4	88	-	-	-
29	 **2 5**	3	**A**	5	83	-	-	-
30	 **2 7**	3	**A**	5	85	-	-	-
32	 **16**	3	**A**	5	-	-	-	69 **1 8**
35	 **2 3**	2	**A**	1	78	-	-	1 **1 8**
36	 **1 7**	3	**A**	18	77 (90)	9	-	14 **1 7**

[a] Entries not listed can be found in the full table in Supporting Information. Reaction conditions: (**A**) "dry" − 4 Å sieve, dry DCM, room temperature, under dry N_2; (**B**) "wet" − DCM, room temperature, open to atmosphere or addition of 1 equiv of H_2O. [b] Parentheses indicate yield based on recovered starting material.

Dibenzylglucosamine **1** was chosen as a representative complex substrate containing multiple protecting groups. Reaction with 1 equiv of NIS in the presence of sieves did not proceed to completion (50% monodebenzylated product **2** after 4 d, entry 1). Two equivalents of NIS (entry 2) gave 59% **2** with concomitant formation of monodebenzylated 3-*O*-benzoyl **3** (37% after 20 h) in a combined monodebenzylation yield of 96%. Prolonged treatment, Lewis acid (TESOTf), or base (TTBP) reduced yield (entries 3−5). Increasing NIS levels further (3 equiv) increased yield and rate (entry 7, **2** and **3** formed in 50% after 4 h), allowing quantitative overall monodebenzylation of **1**. When coupled with secondary Zemplén deprotection, **2** was obtained in an excellent 98% overall yield from **1** (entry 8). Monobenzoyl-monobenzyl sugar **3** could also be obtained through separation in 50% yield using this route.

Scheme 1



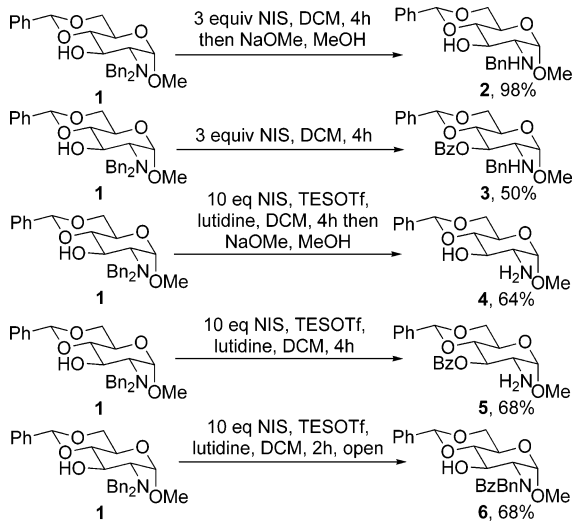
Onset of NIS-mediated reaction was manifested by the development of a maroon color typical of I_2. To establish whether I_2 was effecting debenzylation, **1** was treated directly with I_2 but showed no reaction (even up to 3 equiv); repetition with base TTBP showed only poor debenzylation (54% **2** after 48 h, Entry 10).

Formation of benzamide **6** after prolonged reaction (20 h rather than 4) of **1** with 3 equiv of NIS (entry 9) interestingly indicated that, as well as allowing efficient monodebenzylation, other products might result from the NIS deprotection system through suitable tuning of conditions. Indeed, prolonged reaction (20 h) of **1** with 6 equiv of NIS and 1 equiv of water (entry 11) gave **6** in 46% and for the first time the didebenzylated product **5** (21%). Indication of didebenzylation was a highly promising addition to the NIS deprotection protocol and was improved. Greater excess of NIS (10 equiv) increased formation of **5** (58% **6** and 33% **5**, entry 12; 52% **5** and 39% **6** with added water, entry 13). Prolonged reaction time (1 week, entry 14) gave solely **6** (50%) at the expense of **5**. Additives again proved key: 10 equiv of NIS, 0.5 equiv of TESOTf, 1 equiv of lutidine, and shorter reaction time of 4 h gave 68% didebenzylated sugar **5** and 30% **6** from **1** (entry 15). Sequential coupling with Zemplén deprotection gave a method for didebenzylation of **1** in a workable overall yield of **4** of 64% (entry 16). Added water gave more **6**; 68% of **6** was obtained from **1** with 10 equiv of NIS, 0.5 equiv of TESOTf, 1 equiv of lutidine under moist conditions and in a shortened reaction time of only 2 h (entry 17).

Having established conditions for the preparation of five differentially protected products from **1** simply by tuning conditions (Scheme 2), we next explored other substrates. Formation of monobenzoyl-monobenzyl **3** from **1** clearly necessitated participation of neighbouring OH-3. To investigate the need for a neighboring OH group, as is the case for some *O*-debenzylations,[10] **1** was converted to 3-*O*-silyl ether **7** (97%). Treatment of **7** with the monodebenzylation condi-

(10) Madsen, J.; Viuf, C.; Bols, M. *Chem. Eur. J.* **2000**, *6*, 1140.

Scheme 2



tions determined for **1** (3 equiv of NIS, 4 h) smoothly effected monodebenzylation to **8** (87%, entry 18). Clean deprotection of **8** with TBAF gave **2** in 95%; the three-step conversion of **1** → **7** → **8** → **2** represents an effective (80% overall) alternative to direct monodebenzyation of **1**.

Treatment of **7** under conditions for didebenzylation (10 equiv of NIS) gave **9** in 63−72% (entries 19 and 20).[11] Moreover, debenzylation of monobenzylamine **8** successfully gave fully debenzylated **9** in 79% yield after 24 h (entry 23). Deprotection of **9** with TBAF gave **4** in 73%; three-step conversion **1** → **7** → **9** → **4** represents an effective (62% overall) alternative to the direct monodebenzyation of **1** (64%). Attempts to debenzylate **10** with free OH-6 were sluggish, and the reaction was less clean than for monohydroxyl **1**; 3 equiv of NIS gave a poor 23% of **11** (entry 24). However, treatment of **10** with didebenzylation conditions gave 50% of **12** (entry 25).

Because NIS is also an activator of thioglycoside glycosyl donors in glycosylation reactions[12] we next explored the intriguing potential for one-pot glycosylation-deprotection reactions; initial analyses suggested faster glycosylation than debenzylation at room temperature. Pleasingly, reaction of ethyl thioglucoside donor[13] with dibenzylamine acceptors **1** and **10** using slightly modified monodebenzylation conditions (3 equiv of NIS, 0.5 equiv of TESOTf, 1 equiv of TTBP) successfully gave monodebenzylated coupling products **14** and **15** (Scheme 3)), respectively.[13] Although yields are moderate (35%−42%, 2 steps), access to unusual monobenzylamine disaccharides is useful and highlights the potential for cascade glycosylations using both dibenzylamine donors[7] and acceptors.

(11) Interestingly, treatment of **7** with 5 equiv of NIS, followed by 1 equiv of water (2 h when TLC indicated no **7**) gave **9** in improved 87% yield (entry 21).

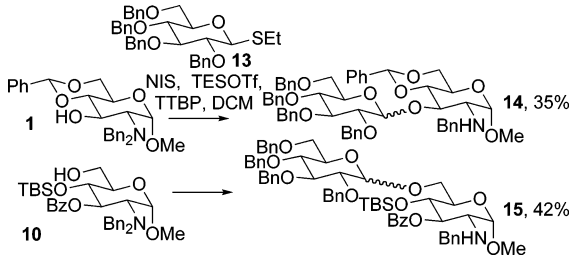
(12) Davis, B. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2137

(13) Low nucleophilicity acceptors gave 47−49% glycosylsuccinimide.

(14) Lower yield of **31** may be from volatility.

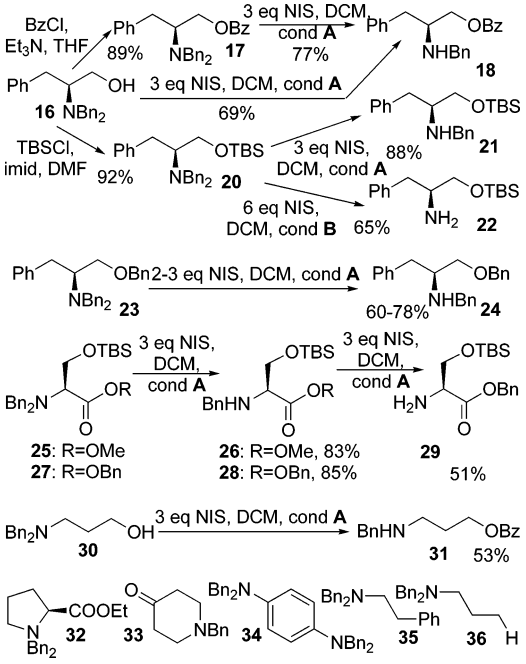
(15) Three equivalents of NIS gave 60% **24** with 20% monodebenzylated-monobenzoylated **18**. *O*-Benzyldecyl ether did not debenzylate with 3 equiv of NIS, and control of NIS (2 equiv) gave more **24** from **23**.

Scheme 3



Applicability to sugars having been demonstrated, non-carbohydrate substrates were investigated (Scheme 4). L-

Scheme 4



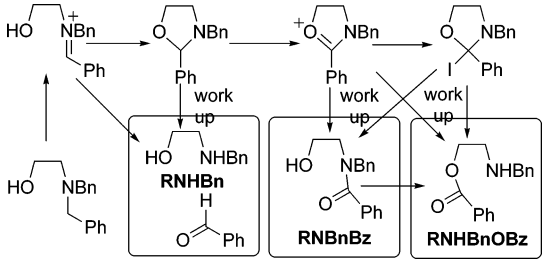
Phenylalanine-derived **20** was monodebenzylated to **21** in 88% (1.5 h, entry 26) and didebenzylated to **22** in 65% yield (entry 28). Various L-serine derivatives were examined next. Methyl ester **25** and benzyl ester **27** both monodebenzylated smoothly (5 h) to give **26** (83%) and **28** (85%), respectively (entries 29 and 30). A second course of monodebenzylation converted **28** in fair yield (51%) to fully debenzylated Ser benzyl ester **29** (entry 31). Substrates containing free hydroxyl groups β and γ to the NBn_2, dibenzylphenylalaninol **16** and γ-dibenzyl alcohol **30**, monodebenzylated with simultaneous benzoylation of OH giving monobenzoyl-monobenzyl amino acids **18** (69%) and **31** (53%), respectively (entries 32 and 33).[14]

Usefully, selectivity over and hence compatibility with *O*-benzyl ethers[10] was possible: tribenzylated **23** was chemoselectively monodebenzylated on nitrogen in 78% (entry 35).[15] Compatibility with *O*-benzoyl protection was also demonstrated: **17** with 3 equiv of NIS gave 77% **18**

(18 h). Interestingly, L-Phe-derived substrates **17**, **20**, and **23,** which differ only in *O*-protection, showed ordered reactivities (OBn > OTBS > OBz) perhaps suggesting a Lewis base type role for O-1 with a neighboring amino substituent during critical rate-limiting step(s).

The ability of NIS to provide tuneable debenzylation opens intriguing mechanistic possibilities. Monitoring of the reaction of **1** with 3 equiv of NIS for 20 h (entry 9) by TLC[16] showed sequential formation of monobenzyl **2** (5−20 min); **2** and monobenzylmonobenzoyl **3** (45 min to 2.5 h); and **2**, **3**, and monobenzylmonobenzamide **6** (20 h). In many crude ^{1}H NMR spectra, benzaldehyde was detected, suggesting hydrolytic formation upon workup. The most plausible mechanism involves benzyliminium formation before hydrolysis or intramolecular nucleophilic trapping by neighboring *O*-substituents prior to collapse to debenzylated products in the presence of adventitious water or upon workup.[17] A speculative mechanistic outline is shown in Scheme 5.

Scheme 5



All successful debenzylations involved substrates with neighboring oxygenated *O*-substituents −OR (R = H, Bn, TBS, Bz). Treatment of substrates **32**−**36** did not result in efficient debenzylation, e.g., **30** successfully debenzylates, but deoxygenated analogue **36** does not. Neighboring *O*-substituents may act as intramolecular Lewis bases/nucleophilic catalysts. Cyclic acetal intermediates have been proposed in the *O*-debenzylation of sugars[10] with neighboring OH groups; migration products observed here for substrates with free alcohol substituents (e.g., **3** from **1**) may support a similar mechanism.

In summary, use of NIS allows tuneable *N*-debenzylation of benzylamine substrates that also contain *O*-functionality; 3 equiv of NIS under dry conditions monodebenzylates, whereas >3 equiv in the presence of adventitious water didebenzylates.

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Supporting Information Available: General experimental details, characterization data, and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Products detected by TLC not necessarily present in the reaction mixture and may be the result of hydrolysis of intermediates.

(17) Interestingly, reaction of **7** with 3 equiv of NIS for 3 h gave a weak, transient EPR signal showing a nitrogen 1:1:1 triplet signal (g = 2.0053, a(N) = 1.55 mT at 9.414 GHz) consistent with a nitrogen centered radical/radical cation (a) [Landoh-Bornstein, A.: Fischer, H., Hellwege, I.-H., Eds.; Springer-Verlag: Berlin, 1985; Vol. 9, Part d. (b) Martin Goez, M.; Sartorius, I. *J. Am. Chem. Soc.* **1993**, *115*, 11123. (c) Shaffer, S. A.; Martin Sadílek, M.; Tureček, F. *J. Org. Chem.* **1996**, *61*, 5234] and might suggest alternative pathways. However, identical reaction outcomes were found in the absence of light, and attempts to trap putative radical intermediates, e.g., 2.5 equiv of methyl methacrylate, failed. Further mechanistic details are currently under investigation.