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Photo Amidoglycosylation of an Allal Azidoformate. Synthesis of β-2-Amido Allopyranosides

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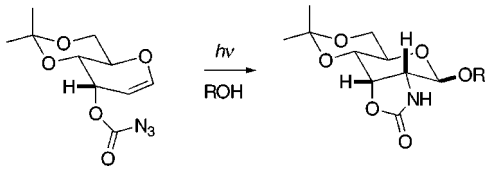
ABSTRACT



Photolysis of an allal C-3 azidoformate provoked intramolecular nitrene insertion into the glycal C═C unit and allowed direct incorporation of alcohol nucleophiles as β-disposed substituents at C-1. The 2-amido allopyranoside products were elaborated via *N*-acylation and selective oxazolidinone hydrolysis, providing *N*-Boc-protected 2-amino sugars and simplifying stereochemical assignments. Synthesis of the potentially labile allal azidoformate was achieved via reaction of the corresponding carbonyl imidazolide with trimethylsilyl azide, facilitated by dibutyltin oxide.

Glycals are attractive starting materials for the preparation of 2-amino sugar derivatives.[1] Ideally, the process leading to C-2−N bond formation should permit in situ glycosylation, but many of the commonly employed methods require subsequent manipulation to generate a useful glycosyl donor. Posing an additional synthetic challenge are target structures that demand installation of nitrogen on the more encumbered glycal face, cis to an axial C-3 substituent.[2] The dual 2-acetamido allopyranose units of the chitinase inhibitor allosamidin (**1**, Figure 1)[3] offer a prime example.

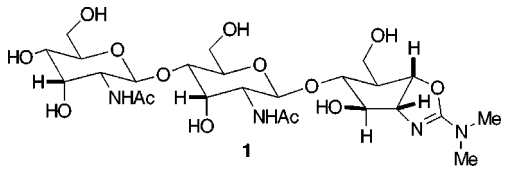


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Figure 1. The chitinase inhibitor allosamidin.

We have pursued an intramolecular strategy that utilizes an azidoformate-derived acyl nitrene as an electrophilic nitrogen source[4] and generates what we presume to be the

(1) For a variety of approaches, see: (a) Du Bois, J.; Tomooka, C. S.; Hong, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 3179. (b) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 5811. (c) Lafont, D.; Boullanger, P.; Carvalho, F.; Vottero, P. *Carbohydr. Res.* **1997**, *297*, 117. (d) Leblanc, Y.; Fitzsimmons, B. J.; Springer, J. P.; Rokach, J. *J. Am. Chem. Soc.* **1989**, *111*, 2995. (e) Lemieux, R. U.; Ratcliffe, R. M. *Can. J. Chem.* **1979**, *57*, 1244. (f) Di Bussolo, V.; Liu, J.; Huffman, L. G., Jr.; Gin, D. Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 204.

(2) To the best of our knowledge, the only direct route currently available to the allosamine motif from glycal starting materials involves halosulfonamidation, followed by a separate base-induced glycosylation step (see ref 1b).

(3) For a review of isolation, biological activity, and synthesis of the allosamidins and allosamidin analogues, see: Berecibar, A.; Grandjean, C.; Siriwardena, A. *Chem. Rev.* **1999**, *99*, 779.

(4) The use of acyl nitrenes for glycal amidation in an intermolecular sense has been explored by Descotes. Those early studies showed, for instance, that mixtures of α- and β-2-amidoglycosides were produced from the photolytic reaction of carbethoxynitrene with tri-*O*-acetyl-D-glucal in the presence of alcohols: (a) Kozlowska-Gramsz, E.; Descotes, G. *Tetrahedron Lett.* **1981**, *22*, 563. (b) Kozlowska-Gramsz, E.; Descotes, G. *Can. J. Chem.* **1982**, *60*, 558.

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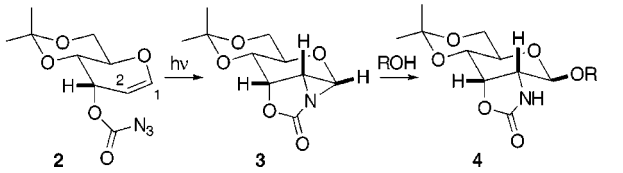
transient aziridine intermediate **3** as a highly activated donor for β-glycosylation (Scheme 1).[5,6] This Letter details prepa-

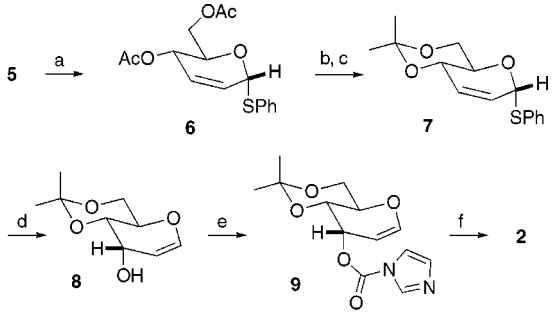
Scheme 1



ration and amidoglycosylation reactions of the potentially labile C-3 allal azidoformate **2**. Additionally, selective cleavage of the oxazolidinone and acetonide functions of the amidoglycosylated products **4** is possible, enhancing the utility of **2** as an allosamine synthon.

The necessary allal **8** for our allylic azidoformate synthesis was prepared as detailed in Scheme 2. Starting from tri-*O*-

Scheme 2[a]



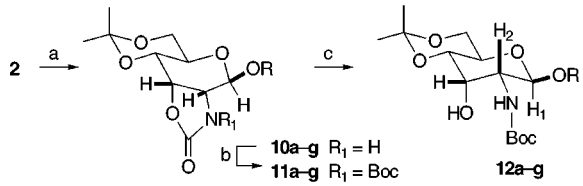
[a] Key: (a) PhSH, $SnCl_4$, CH_2Cl_2, −20 °C, 25 min, 74%; (b) K_2CO_3, 5/1 MeOH/CH_2Cl_2, 0 °C, 75 min, 98%; (c) $H_2CC(OMe)Me$, PPTs, CH_2Cl_2, 23 °C, 3 h, 85%; (d) *m*-CPBA, CH_2Cl_2, 0 °C, 15 min then piperidine, THF, 23 °C, 90 min, 87%; (e) 1,1′-carbonyldiimidazole, CH_2Cl_2, 23 °C, 75 min; (f) $TMSN_3$, *n*-Bu_2SnO (0.2 equiv), THF, 23 °C, 8 d, 51% (2 steps).

acetyl-D-glucal (**5**), Ferrier substitution[7] formed α-phenylthioglycoside **6**.[8] After introduction of the 4,6-*O*-isopropylidene protection,[8] oxidation of **7** at sulfur triggered allylic sulfoxide to sulfenate rearrangement,[9] yielding the desired axial C-3 alcohol **8** upon interdiction of the sulfenate by the thiophile piperidine.[10]

A vinylogous anomeric effect[11] destabilized activated acyl derivatives of alcohol **8**, complicating its conversion to azidoformate **2**. For example, formation of the *p*-nitrophenyl carbonate[5a] from alcohol **8** induced elimination of the C-3 substituent with extrusion of CO_2 and *p*-nitrophenoxide. In contrast, carbonyl imidazolide **9** formed smoothly. The lability of **9**, which was unstable to silica gel chromatography, required an alternative to the usual acid-mediated procedure for conversion of carbonyl imidazolides to acyl azides.[5b,12] Ultimately, we discovered that trimethylsilyl azide in the presence of di-*n*-butyltin oxide effected the desired transformation.[13,14] Azidoformate **2** decomposed on mildly acidic silica gel (Merck 60, 230−400 mesh), but was isolated in reliable yields after aqueous workup and rapid chromatography using neutral (Davisil) silica.[15] Once purified, **2** was a crystalline solid, stable for months at room temperature.[16]

Photochemical amidoglycosylation studies engaged allal azidoformate **2** as an incipient glycosyl donor. Irradiation of **2** in methylene chloride solutions containing an alcohol as the glycosyl acceptor permitted isolation of the corresponding β-2-amido allopyranosides **10a**−**g** (Scheme 3 and

Scheme 3[a]



[a] Key: (a) *hν* (254 nm, Vycor filter, Rayonet merry-go-round apparatus), ROH (3−5 equiv), CH_2Cl_2, 23 °C; (b) Boc_2O, Et_3N, DMAP, THF, 23 °C; (c) LiOH·H_2O, 3/1 THF/H_2O, 23 °C.

Table 1). Best results were obtained using 3−5 equiv of freshly purified glycosyl acceptor. Where the excess glycosyl acceptor could be removed completely under reduced pressure (entries a−c), the crude photolysis products were examined by ^{1}H NMR to assess β:α selectivity. In none of

(5) Bergmeier has demonstrated intramolecular formation of isolable acyl aziridines by thermolysis of allylic azidoformates as a route to β-amino alcohols, and Bach has explored an iron(II)-mediated version of the Bergmeier process: (a) Bergmeier, S. C.; Stanchina, D. M. *J. Org. Chem.* **1999**, *64*, 2852. (b) Bergmeier, S. C.; Stanchina, D. M. *J. Org. Chem.* **1997**, *62*, 4449. (c) Bergmeier, S. C.; Stanchina, D. M. *Tetrahedron Lett.* **1995**, *36*, 4533. (d) Bach, T.; Schlummer, B.; Harms, K. *Chem. Commun.* **2000**, 287.

(6) For other recent examples of intramolecular insertion reactions of acyl nitrenes with olefins, see: (a) Williams, D. R.; Rojas, C. M.; Bogen, S. L. *J. Org. Chem.* **1999**, *64*, 736. (b) de Santis, M.; Fioravanti, S.; Pellacani, L.; Tardella, P. A. *Eur. J. Org. Chem.* **1999**, 2709. (c) Koohang, A.; Stanchina, C. L.; Coates, R. M. *Tetrahedron* **1999**, *55*, 9669.

(7) Ferrier, R. J.; Prasad, N. *J. Chem. Soc. C* **1969**, 570.

(8) Valverde, S.; García-Ochoa, S.; Martín-Lomas, M. *J. Chem. Soc., Chem. Commun.* **1987**, 383.

(9) (a) Wittman, M. D.; Halcomb, R. L.; Danishefsky, S. J. *J. Org. Chem.* **1990**, *55*, 1979. (b) Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147.

(10) All new compounds were characterized by a combination of ^{1}H and ^{13}C NMR, IR, HRMS, and combustion analysis. For details, see the Supporting Information.

(11) For a discussion of the vinylogous anomeric effect and leading references, see: (a) Curran, D. P.; Suh, Y.-G. *Carbohydr. Res.* **1987**, *171*, 161. (b) Denmark, S. E.; Dappen, M. S.; Sear, N. L.; Jacobs, R. T. *J. Am. Chem. Soc.* **1990**, *112*, 3466.

(12) Yuan, P.; Plourde, R.; Shoemaker, M. R.; Moore, C. L.; Hansen, D. E. *J. Org. Chem.* **1995**, *60*, 5360.

(13) For the use of this combination in tetrazole synthesis, see: Wittenberger, S. J.; Donner, B. G. *J. Org. Chem.* **1993**, *58*, 4139. In accord with this report, we observed that in reactions with **9** and $TMSN_3$ the dibutyltin oxide dissolved over a period of several hours, possibly forming an *O*-trimethylsilyl azidostannylhydrin as the reactive source of azide. Wittenberger has accumulated evidence for such an intermediate using ^{119}Sn NMR spectroscopy.

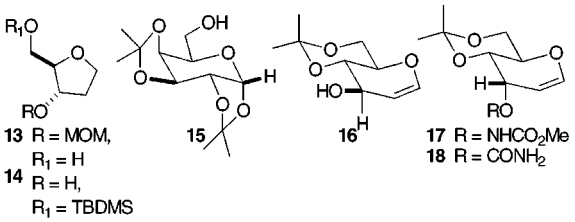
Table 1. Formation and Derivatization of Amidoglycosylation Products from Allal Azidoformate **2**

entry	ROH (equiv)	**2** → **10**, % yield[a]	**10** → **11**, % yield[a]	**11** → **12**, % yield[a]	J_{12} for **12** (Hz)
a	MeOH (5.0)	40	62	64	8.4
b	EtOH (5.0)	38	80	80	8.1
c	*i*-PrOH (4.9)	35[b]	55	94	8.4
d	**13**[c] (3.0)	15 (37[d])	60	57	8.4
e	**14**[c] (3.5)	10 (23[d])	47	>95	8.4
f	**15** (5.0)	11 (<5[e])	79	77	8.8 (3.7[e])
g	**16** (4.9)	7	62	71	8.4

[a] Isolated yield after silica gel chromatography. [b] Yield was 32% with 2.5 equiv of *i*-PrOH and 22% using 1.5 equiv of *i*-PrOH. [c] Prepared by hydrogenation (H_2, Pd/C) of the corresponding furanoid glycal. See ref 18 for furanoid glycal synthesis. [d] Yield in parentheses is based on recovered alcohol. [e] Value in parentheses is for the α-anomer.

these cases did we identify diastereomeric amidoglycosylated products, and a single 2-amido allopyranoside, shown to be the β-anomer (vide infra), was isolated after chromatography.[17] With nonvolatile, sugar-derived alcohols as glycosyl acceptors, unreacted alcohol could be recovered after the photolysis (entries d and e).

The efficiency of amidoglycosylation of **2** with low molecular weight alcohols (entries a−c) was reasonable, given the two-step, one-pot nature of the process, but yields were lower in more challenging cases where the primary and secondary hydroxyls of sugar derivatives were used as glycosyl acceptors (entries d−g). Both sterically and electronically, the saccharide acceptor sites are less reactive than in the simple alcohol models, and the acceptors include more functionality for side reactions with the intermediate acyl nitrene. For example, reaction with glycal **16**[19] provided only a minor amount of amidoglycosylation product **10g**. Instead, the nitrene from **2** added in *intermolecular* fashion to the double bond of **16**, generating a donor for glycosylation of the hydroxyl on a second molecule of **16**. Nevertheless, β-2-amido allopyranosides **10**, which would be difficult to access otherwise, are available directly from glycal azidoformate **2**. To develop broader synthetic utility we are investigating amidoglycosylation via low-temperature photolysis and transition metal-promoted nitrene formation.[5d]

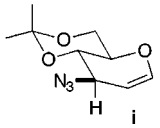


Minor byproducts in the photolysis reactions were isolated and identified as *N*-alkoxyurethanes (e.g., **17**), formed upon Curtius rearrangement of the acyl nitrene and addition of alcohol to the resulting alkoxy isocyanate.[20,21] In addition, we characterized carbamate **18** which may have arisen via sequential hydrogen atom abstraction by a triplet nitrene.[20] The mass balance in these reactions consisted of complex mixtures of more polar material, as revealed by ^{1}H NMR analysis after thorough chromatography. A control experiment showed that azidoformate **2** did not react with 2-propanol in the absence of UV light.

Both to establish conclusively the anomeric center stereochemistry and to probe the utility of the cyclic carbamate *N*-protection, selective opening of the oxazolidinone ring in amidoglycosylated products **10a**−**g** was undertaken. *N*-Acylation with di-*tert*-butyl dicarbonate provided Boc derivatives **11** which were readily hydrolyzed[5a,22] at the internal carbonyl,[23] providing *N*-Boc-protected amino sugars **12a**−**g**. The pyranose ring now assumed the chair conformation, and the β-orientation of the glycosidic bond at C-1 was confirmed by examination of J_{12} values (Table 1).[24]

Finally, we were able to cleave the acetonide protecting group without disturbing the anomeric position, as readily demonstrated for the conversion of 2-amido glycoside **10c** to diol **19** in acidic methanol, followed by careful bicarbonate quench (Scheme 4).[25] Masking the primary alcohol as a silyl ether provided **20**, bearing a free C-4 hydroxyl group as a potential glycosyl acceptor site for disaccharide synthesis.

(14) Without dibutyltin oxide, reaction of **9** required a large excess (10 equiv) of $TMSN_3$ in refluxing THF. Under these forcing conditions, diastereomerically pure allyl azide **i** was the major product. Only limited amounts (10−15%) of byproduct **i** were formed with *n*-Bu_2SnO as an additive. Experiments to optimize and explore the generality of this method for azidoformate synthesis are in progress.



i

(15) For instances of Davisil silica used in the purification of acid-sensitive saccharides, see the Supporting Information for the following paper: Roush, W. R.; Bennett, C. E. *J. Am. Chem. Soc.* **2000**, *122*, 6124.

(16) **CAUTION!** Azidoformates are potentially explosive. While we have encountered no difficulties with the preparation and use of azidoformate **2**, appropriate safety precautions are strongly recommended. For a dramatic report on the instability of a lower molecular weight azidoformate during distillation, see: Feyen, P. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 115.

(17) Our attempts to observe glycosyl aziridine **3** by conducting the photolysis in the absence of alcohol and examining the reaction mixture by ^{1}H NMR have been unsuccessful.

(18) (a) Ireland, R. E.; Wilcox, C. S.; Thaisrivongs, S. *J. Org. Chem.* **1978**, *43*, 786. (b) Cheng, J. C.-Y.; Hacksell, U.; Daves, G. D., Jr. *J. Org. Chem.* **1985**, *50*, 2778.

(19) Kjølberg, O.; Neumann, K. *Acta Chem. Scand.* **1993**, *47*, 843.

(20) Lwowski, W. In *Azides and Nitrenes: Reactivity and Utility*; Scriven, E. V., Ed.; Academic Press: New York, 1984; pp 205−246.

(21) We favor structure **17** for this byproduct over the isomeric *N*-methoxyurethane (**17** with R = C(O)NHOMe) which might form by direct acyl nitrene insertion into the alcohol O−H bond. The C-3 methine resonance in the ^{1}H NMR spectrum of **17** appears at δ 4.21, well upfield of the corresponding resonance for C-3-*O*-acylated compounds **2** (δ 5.21), **9** (δ 5.40), and **18** (δ 5.16), suggesting that in **17** the −NH− unit insulates the C-3 oxygen from the carbonyl group.

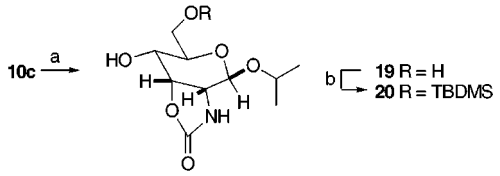
(22) Ishizuka, T.; Kunieda, T. *Tetrahedron Lett.* **1987**, *28*, 4185.

(23) Selective hydrolysis at the internal carbonyl of *N*-Boc-protected oxazolidinones has been a challenge. See, for example: Di Giovanni, M. C.; Misiti, D.; Villani, C.; Zappia, G. *Tetrahedron: Asymmetry* **1996**, *7*, 2277. For LiOH as the base of choice, see ref 5a and citations therein.

(24) In only one case, photolysis of azidoformate **2** with 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose (**15**), was a trace of the α-anomer isolated. *N*-Boc protection and oxazolidinone hydrolysis verified a marked difference in the J_{12} values between β-**12f** and α-**12f** (Table 1, entry f).

(25) Concentration of the acidic reaction mixture without prior neutralization, followed by silica gel chromatography, promoted almost complete inversion of the C-1 stereochemistry (α:β = 16:1 by ^{1}H NMR analysis).

Scheme 4[a]



[a] Key: (a) 5% HCl/MeOH, 23 °C, 40 min, $NaHCO_3$ quench; (b) TBDMSCl, imidazole, CH_2Cl_2/DMF, 23 °C, 30 min, 49% (2 steps).

In summary, we have demonstrated a one-pot amidoglycosylation strategy based on light-initiated acyl nitrene formation from a glycal azidoformate. This tandem sequence employs internal nitrene delivery for amidation of the more encumbered olefin face and has allowed us to prepare a variety of otherwise elusive β-2-amido allopyranosides. Ultimately, we envision providing for iterative construction of more elaborate amino sugar frameworks, including the allosamidin disaccharide.

Acknowledgment. We are grateful for generous financial support from Research Corporation (Cottrell College Science Award); the Petroleum Research Fund, administered by the American Chemical Society; and Barnard College. We also thank the Bernice Segal Fund (M.P.), the Hughes Foundation (C.M.L. and S.E.T.), the Council on Undergraduate Research (C.K.), and the Pew Foundation (C.M.R.) for research fellowships and Ms. Abigail Smenton for assistance in preparation of the manuscript. The Barnard College NMR facility is supported by a grant from the National Science Foundation (NSF DUE-9952633).

Supporting Information Available: Experimental procedures and characterization data for compounds **2**, **6**−**9**, **10a**−**g**, **11a**−**g**, **12a**−**g**, and **17**−**20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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