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A Versatile, Three-Component-Reaction Route to *N*-Glycosylamines[§,1]

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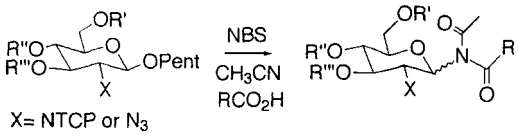
ABSTRACT



Under the agency of *N*-bromosuccinimide, *n*-pentenyl glycosides, acetonitrile, and carboxylic acids participate in three-component-reactions that afford N-acylated glycosylamines. The procedure tolerates diverse donors, and C2-tetrachlorophthalimido and C2-azido groups effectively control anomeric stereoselectivity. Success of the procedure does not appear to depend on the acid's strength, but for an aromatic acid, substitution pattern affects the rate, while the presence of a lone pair on the para substituent inhibits the process.

Glycoproteins are ubiquitous bioregulators in nature,[2] and the fact that these glycoconjugates influence protein shape and function is firmly established.[3] The subclass in which the glyco/protein conjugation is through an anomeric nitrogen, as symbolized by **1**, is arguably the most widespread of these bioregulators[4,5] and is associated with major health disorders, including HIV infection,[6] tuberculosis,[7] paroxysmal hemoglobinuria,[8] and transmissible spongiform encephalopathies.[9] This coincidence has therefore inspired novel innovations for laboratory preparation of biological constructs.[10,11] Our own laboratory has contributed a procedure, expressed retrosynthetically in Scheme 1,[12] which had been designed specifically for high mannose glycoproteins. However, the insurgence of combinatorial chemistry[13] and the

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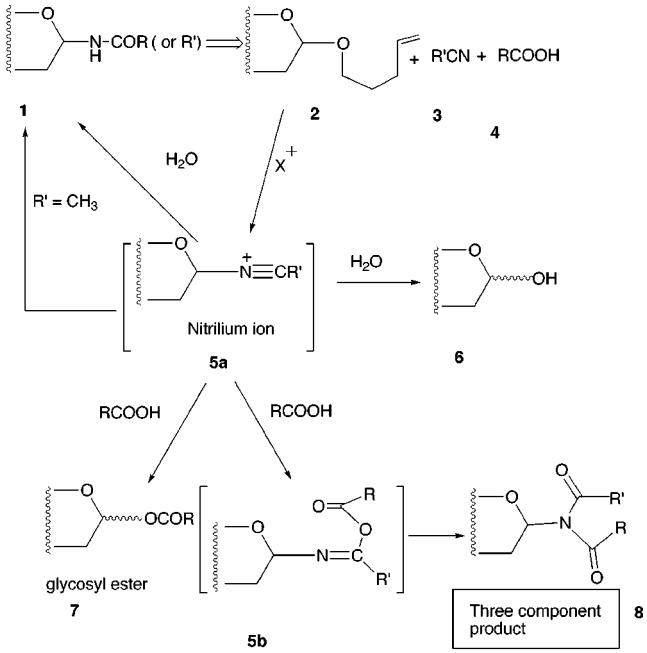
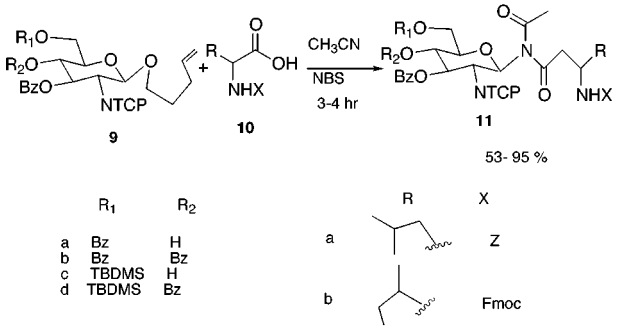
Scheme 1



efficiency of multicomponent reactions[14] have encouraged us to explore the versatility of Scheme 1, in the context of glycosylamine diversity, and some of our findings are reported herein. In addition to the preparative value, the results of this three-component-reaction study provide notable insights into glycosyl reactivity and anomeric stereocontrolling factors.

For most N-linked glycoproteins, the first sugar is a 2-amino-2-deoxy glucosyl derivative, and the linkage is usually β-oriented.[4] For initial exploratory studies, the recently introduced tetrachlorophthaloyl (TCP) protecting group[15] was chosen because it fosters β-selectivity and is readily cleaved.[16] To level the playing field in these initial studies, only β-donor substrates **9a**−**d** were used, and acetonitrile[17] was chosen as the solvent/reactant. Preliminary experiments showed that the potent iodonium source (NIS/TESOTf)[18] gave poor results, whereas NBS proved to be satisfactory. Coupling with Z-leucine and FMOC isoleucine (**10a** and **10b**, respectively) gave good to excellent yields of three-component-reaction products **11** in 53−95% yields (Scheme 2).[19]

Scheme 2



From Scheme 1, the fate of the key nitrilium intermediate **5a** is seen to depend on several variables. The "reactivity" of the carboxylic acid **4** is clearly of primary interest, since capture of **5a** leads to the desired three-component-reaction product **8**, whereas displacement leads to the glycosyl ester **7**. For insight into the impact of the acid's reactivity, we tested a variety of benzoic acids, grouped as structures **12**−**15**, having a range of acidities, resonances, and inductive effects.[20]

The most obvious result in Table 1 is the complete absence of three-component-reaction products with **12a**−**d** (entries i−iv). This appears to be related to the para lone pairs on acids **12a**−**d** since *o*-chloro benzoic acid reacts well.[12c] This indicates that the ortho vs para locations of the substituent is important in +M substituents. In the case of **12b**, considerable amounts of glycosyl ester (cf. **5**) were obtained. Acidity does not have an impact on the outcome of the reaction; the pK_a range, which runs from ∼4 for **13c** (entry viii) to ∼2.2 for **14a** (entry ix),[20] seems to have little impact on the *success* of the three-component reaction judging from the yields of 95% and 88%, respectively. However, with regard to the rates of couplings, the uniformly slow reactions in entries xiii−xvii correlate, curiously, with the *m*-nitro-substituted benzoic acids **15a**−**c**. In this context, it should

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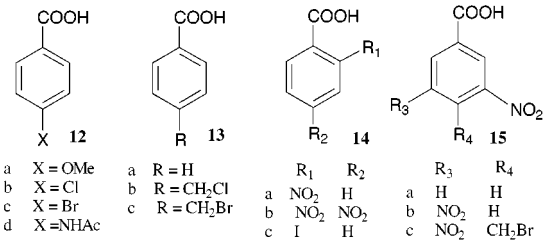
Table 1. Three Component Reactions with Aromatic Acids



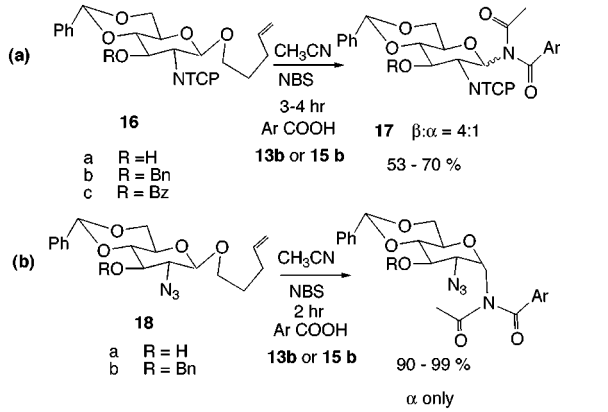
entry	acid	substrate	yield (%)	time (h)
(i)	**12a**	**9d**	No three component products	
(ii)	**12b**	**9d**		
(iii)	**12c**	**9d**		
(iv)	**12d**	**9d**		
(v)	**13a**	**9d**	62	4
(vi)[a]	**13b**	**9d**	32	1.5
(vii)	**13b**	**9b**	53	3.5
(viii)	**13c**	**9b**	95	7
(ix)	**14a**	**9b**	88	3
(x)	**14b**	**9b**	67	6
(xi)[a]	**14b**	**9d**	poor	
(xii)[a]	**14c**	**9d**	56	3
(xiii)	**15a**	**9b**	60	8
(xiv)	**15b**	**9b**	68	6
(xv)[a]	**15b**	**9d**	26	8
(xvi)	**15c**	**9d**	70	7

[a] These reactions gave evidence of TBDMS cleavage. Longer reaction time for entry (vi) didn't improve the yield.

be noted that longer reaction times frequently led to decomposition, particularly loss of the TBDMS protecting group in substrate **9d** (entries xi and xv), and hence to lower yields.

The results in Scheme 3 are particularly instructive on the question of anomeric stereocontrol. The influence of torsional effects for generating armed/disarmed glycosyl donors was noted earlier by our group,[21] and the principle has been skillfully applied recently by Ley and co-workers.[22] Torsional effects also affect α/β stereocontrol[23] and the ability of the 4,6-*O*-benzylidene ring to induce α-selectivity in glycosylation reactions has been featured in recent work of Crich and co-workers.[24] The latter influence is clearly apparent when the results with **9** and **16** are compared. Thus, the fact that α-products are not detectable in the reaction of **9** but comprise approximately 20% for the products from **16** is a telling example of the 4,6-*O*-benzylidene ring's ability to compromise the β-directing neighboring group participation of the TCP moiety in **16**.

Scheme 3



Since the seminal work of Paulsen 20 years ago,[25] C2-azides have been favored for α-stereocontrol in coupling reactions. Not surprisingly therefore, the combination of the acetal with the C2 azide moiety in donors **18a** and **18b** leads to α-products exclusively, in virtually quantitative yields.

In summary, the three-component reaction to give glycosylamines accommodates a wide range of glycosyl donors and carboxylic acids and offers the ability to produce naturally occurring β-analogues (Scheme 2) or unnatural α-counterparts (Scheme 3b) with complete stereocontrol. The results in Table 1 (a) do not show any correlation with pK_a's of the acids, (b) suggest that *o*-nitrobenzoic acids react faster than *m*-nitro analogues (entry ix versus xiii), and (c) indicate that acids bearing a lone pair at the para position, must be avoided. Further studies are underway to clarify and extend these observations.

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

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