GLYCOSYL PHOSPHORAMIDIMIDATES AS VERSATILE GLYCOSYL DONORS

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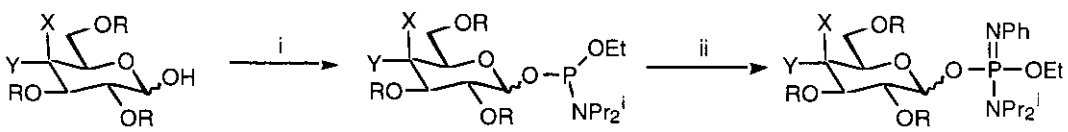
Abstract - A Staudinger reaction of glycosyl phosphoramidites with phenyl azide provides an efficient procedure to access phosphoramidimidates. Their application as glycosyl donors in glycosidation is also described.

Studies have shown that the leaving group of glycosyl donor plays a dominant role in both stereoselectivity and the yield of glycosidations.[1] Among the various glycosyl donors available,[2] phosphorus-containing derivatives[3-5] such as glycosyl phosphoramidates[3] and phosphites[5] have been demonstrated to be very effective donors in yielding a stereocontrolled glycosidation. Focusing our attention on the leaving groups, we envisioned that the availability of new phosphorus (V) derivatives as leaving groups will enable us to fine tune the reactivity of the glycosyl donors by simple modification of the phosphorus substituents. In preparation of these glycosyl donors, one of the substituents can be introduced by reaction of glycosyl phosphoramidites (**2**) with alkyl or aryl azides[6] to give glycosyl phosphoramidimidates (**3**).

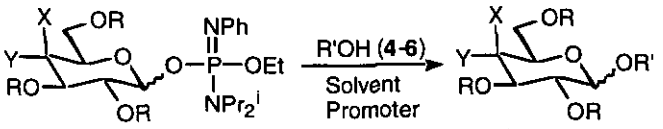
Herein, we describe a procedure for preparation of phosphoramidimidates (**3**) and their use in subsequent glycosidation with various glycosyl acceptors (**4-6**). Methyl-protected and benzyl-protected glycopyranosyl phosphoramidites (**2**) (Scheme 1) were readily prepared by condensation of the corresponding pyranoses (**1**) with ethoxy bis(diisopropylamino)phosphine (1.2 equiv.) in the presence of diisopropylammonium tetrazolide (1.5 equiv., CH_2Cl_2, room temperature, 12 h).[8] Treatment of (**2**) with phenyl azide in benzene at 45 °C gave (**3**), which can be directly used as glycosyl donors after removal of solvent without further purification. These glycosyl donors are stable at -15 °C for several months without any appreciable deterioration and were employed in the following glycosidations. In our investigation, two solvents (CH_2Cl_2 or EtCN), and two promoters (TMSOTf and $BF_3{\cdot}OEt_2$) defined the parameters of glycosidation, the results of which are summarized in Table.



1 **2** **3**

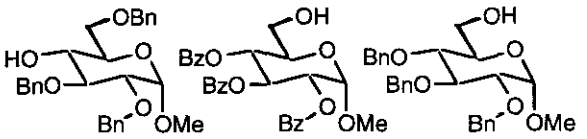
a: X = H, Y = OMe, R = Me; **b**: X = OMe, Y = H, R = Me; **c**: X = OBn, Y = H, R = Bn.

Scheme: i) $EtOP(NPr_2^i)_2$ (1.2 eq.), diisopropylammonium tetrazolide (1.5 eq.), CH_2Cl_2, room temperature, 12 h.; ii) PhN_3 (1.2 eq.), PhH, 45 °C, 2 h.



(3) (7-12)

3a: X = H, Y = OMe, R = Me;
3b: X = OMe, Y = H, R = Me;
3c: X = OBn, Y = H, R = Bn.



(4) (5) (6)

Table. Glycosidation[a] of Phosphoramidimidates (**3a-c**) with Alcohols (**4-6**)

Entry	Acceptor	Donor[b]	Promoter	Solvent	Product	Yield[c]	α:β[d]
1	**4**	**3a**	TMSOTf	EtCN	**7**	35	1:1.3
2	**4**	**3a**	TMSOTf	CH_2Cl_2	**7**	41	1:0.7
3	**4**	**3a**	$BF_3{\cdot}OEt_2$	EtCN	**7**	48	1:2.0
4	**4**	**3a**	$BF_3{\cdot}OEt_2$	CH_2Cl_2	**7**	62	1:0.5
5	**4**	**3c**	TMSOTf	EtCN	**8**	53	1:6.1
6	**5**	**3a**	TMSOTf	EtCN	**9**	43	1:2.2
7	**5**	**3a**	TMSOTf	CH_2Cl_2	**9**	76	1:0.9
8	**5**	**3a**	$BF_3{\cdot}OEt_2$	EtCN	**9**	50	1:20
9	**5**	**3a**	$BF_3{\cdot}OEt_2$	CH_2Cl_2	**9**	76	1:2.7
10	**6**	**3a**	TMSOTf	EtCN	**10**	73	1:20
11	**6**	**3a**	TMSOTf	CH_2Cl_2	**10**	43	1:20
12	**6**	**3a**	$BF_3{\cdot}OEt_2$	EtCN	**10**	51	1:13
13	**6**	**3a**	$BF_3{\cdot}OEt_2$	CH_2Cl_2	**10**	56	1:4.3
14	**6**	**3b**	TMSOTf	EtCN	**11**	94	1:2.7
15	**6**	**3b**	$BF_3{\cdot}OEt_2$	EtCN	**11**	53	1:4.6
16	**6**	**3c**	TMSOTf	EtCN	**12**	81	1:10
17	**6**	**3c**	$BF_3{\cdot}OEt_2$	EtCN	**12**	47	1:7.3

[a] Glycosidation conditions: the reaction was conducted at -78°C with donor/acceptor/promoter molar ratios = 1.2/1.0/1.0. In the case of reactions with $BF_3.OEt_2$, pulverized 4Å molecular sieves (100 mg) was added to the reaction mixture in advance. The reactions were monitored by tlc and typical reaction times = 0.5 - 3.0 h. [b] Anomeric composition α:β = 1:3. [c] Isolated yields are based on the acceptors used. [d] The ratios were determined by 200 MHz ^1H nmr (Gemini, Varian) and hplc (column, Adsorbosphere silica 5u, 4.6 x 250 mm; eluent, 15% ethyl acetate in hexanes; flow rate, 1.5 ml/min; detection, 254 nm).

The β-Selectivities increased dramatically as the acceptor was changed from secondary alcohol (**4**) (α/β:1/1.3) to primary alcohols (**5**) or (**6**) (α/β:1/20, Entries 8, 10-11 in Table) for both TMSOTf and BF_3OEt_2. In general, propionitrile (EtCN) appears to be a better solvent for achieving β-selectivity and the significant effect of the nitrile solvents on stereoselectivities of glycosidation with benzyl-protected glycopyranosyl donors in favor of the predominant formation of β-glycosides is well documented.[3,9] In influencing β-selectivity, $BF_3{\cdot}OEt_2$ and EtCN combination proved superior for acceptor (**5**), whereas TMSOTf proved superior for acceptor (**6**) in either EtCN or CH_2Cl_2. While the mechanistic basis is not clear, TMSOTf-promoted glycosidation of the phosphoramidimidates to give β-selectivity probably proceeds through the intermediacy of the thermodynamically more stable α-D-glycopyranosyl triflate (or its tight α-ion pair) or α-D-glycopyranosyl-nitrilium ion

associated with phosphoramidimidate-triflate complex in the presence of EtCN, followed by the backside attack of acceptor alcohol on this intermediate.[3] Although the β-selectivities with tested phosphoramidimidates have been noted to be modest, barring select cases (Entries 8, 10-11), when compared to other phosphorus-containing leaving groups, the new P(V) derivatives provide potential leads to further modify their reactivities to achieve consistently high β-selectivity.

In conclusion, we have shown the utility of glycopyranosyl phosphoramidimidates as glycosyl donors with a variety of acceptors. The ready preparation of glycosyl phosphoramidimidates *via* Staudinger reaction will allow us to prepare a library of glycosyl donors by simply changing the substituent on phosphorus.

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7. Selected data of ^{1}H (200 MHz, $CDCl_3$) and ^{13}C nmr (50 MHz, $CDCl_3$) for **7-12**: **7**: H-1'α, 5.71 (d, $J_{1',2'}$=3.98 Hz); H-1'β, 4.30 (d, $J_{1',2'}$=7.62 Hz); C-1α, 97.55; C-1'α, 98.31; C-1'β, 104.81. **8:** H-1'α, 5.76(d, $J_{1',2'}$=3.66 Hz); H-1'β not observed due to spectral overlap; C-1'α, 98.2; C-1α, 99.3; C-1'β, 103.6. **9**: H-1'α, 4.91 (d, $J_{1',2'}$=3.50 Hz); H-1'β, 4.29 (d, $J_{1',2'}$=7.68 Hz); C-1'α, 94.12; C-1α, 97.50; C-1'β, 104.17. **10**: H-1'α, 5.23 ($J_{1',2'}$=3.62 Hz); H-1'β, 4.25 (d, $J_{1',2'}$=7.46 Hz); C-1α, 97.55; C-1'α, 98.53; C-1'β, 104.04. **11**: H-1'α, 5.05 (d, $J_{1',2'}$=3.28 Hz); H-1'β, 4.24 (d, $J_{1',2'}$=7.62 Hz); C-1α, 98.39; C-1'α not observed due to weakness of peak; C-1'β, 104.40. **12**: H-1'α not observed due to spectral overlap; H-1β, 4.23 (d, $J_{1',2'}$=4.94 Hz); C-1α, 98.46; C-1'α not observed due to weakness of peak; C-1'β, 104.74.
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