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GLYCOSYL DONORS WITH PHOSPHORIMIDATE LEAVING GROUPS FOR EITHER α- OR β- GLYCOSIDATION

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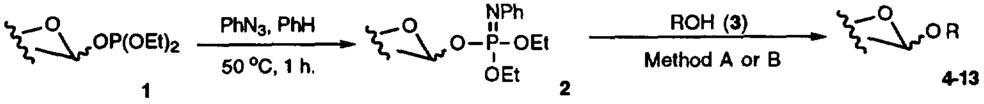
Abstract: Glycosyl *N*-phenyl diethyl phosphorimidates, readily prepared *via* the Staudinger reaction of glycosyl diethyl phosphites with phenyl azide, served as efficient glycosyl donors for the formation of either 1,2-*cis* or 1,2-*trans* glycosidic bonds under selected reaction conditions.

There has been considerable interest in developing novel leaving groups of glycosyl donors for the desired glycosidation with high yield and selectivity.[1] Significant progress has been made in using glycosyl donors that contain halogen, oxygen, nitrogen, and sulfur moieties as leaving groups.[2] The investigation of phosphorus-containing leaving groups includes trivalent and pentavalent phosphorus compounds.[1,3,4] Among the many features that are particularly noteworthy are: (1) glycosidation of an extremely acid-sensitive aglycone in Corey's elegant total synthesis of paeoniflorin,[3b] (2) α-sialylation of sialyl phosphite to provide high yield and stereoselectivity,[3c] and (3) excellent stereocontrol observed in β-mannopyranosylation of mannosyl phosphinothioates. We now report the preliminary results on the glycosylation of glycosyl phosphorimidates [(GlyO)P(OR)$_2$=NPh], readily derived from the Staudinger reaction[5] of phenyl azide with glycosyl phosphites. As an application of this methodology, the selective formation of either 1,2-*cis* or 1,2-*trans* glycosidic bonds is described.

Glycosyl phosphorimidates [(GlyO)P(OR)(OR')=NR"] have the potential to offer a range of "tailor-made" glycosyl donors because of the attachment of three variable substituents on the phosphorus. Another feature in this developing class of glycosyl donors is the simplicity in accessing starting materials. For example, diethyl glycopyranosyl phosphites (**1a-e**) were prepared by the coupling of corresponding glycopyranoses with diethyl *N,N*-diethylphosphoramidite in the presence of 1H-tetrazole.[3a] Treatment of glycosyl phosphites (**1**) with phenyl azide (1.1 equiv.) in benzene (50 °C, 1h) provided the desired glycosyl *N*-phenyl diethyl phosphorimidates (**2**) after removal of the solvent and the remaining phenyl azide *in vacuo*. These gave satisfactory ^{1}H and ^{13}C NMR data,[6,7] with an anomeric composition similar to that of the corresponding starting glycosyl diethyl phosphites.

The crude glycosyl phosphorimidates (**2**) could be used directly in the subsequent glycosidation reactions.

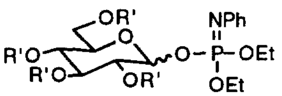


Method A: ROH (0.8 equiv.), Lutidinium *p*-toluenesulfonate (LPTS)/*n*-Bu_4NI (1.2 equiv.), PhH, 4Å MS, 40 °C, 12h;
Method B: ROH (0.8 equiv.), TMSOTf (1.2 equiv.), EtCN, -78 °C, 1h.

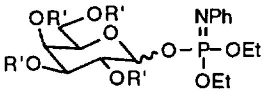
Table. Glycosidation of *N*-Phenyl Diethyl Glycosyl Phosphorimidates **2**.

Entry	Donor[a]	Acceptor	Method	Product	Yield(%)[b]	α:β [c]
1	**2a**	**3a**	(A)	**4**	76	10:1
2	**2b**	**3a**	(A)	**5**	73	5:1
3	**2c**	**3a**	(A)	**6**	73	5.3:1
4	**2d**	**3a**	(A)	**7**	65	4:1
5	**2a**	**3b**	(A)	**8**	68	10:1
6	**2a**	**3a**	(B)	**4**	60	1:30
7	**2b**	**3a**	(B)	**5**	70	1:9
8	**2c**	**3a**	(B)	**6**	83	1:30
9	**2d**	**3a**	(B)	**7**	72	1:5
10	**2a**	**3b**	(B)	**8**	75	1:30
11	**2c**	**3b**	(B)	**9**	68	1:35
12	**2c**	**3c**	(A)	**10**	40	2:1
13	**2c**	**3d**	(B)	**11**	78	1:1.5
14	**2e**	**3a**	(A)	**12**	82	4:1
15	**2e**	**3a**	(B)	**12**	95	3:1
16	**2e**	**3d**	(B)	**13**	82	only α

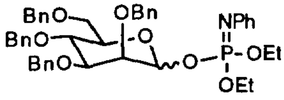
[a] The anomeric composition (α/β) of **2a** (1.8/1), **2b** (2.3/1), **2c** (1.2/1), **2d** (1.1/1),and **2e** (1.1/1). [b] Isolated yields based on acceptors. [c] The ratios were determined by 200 MHz ^1H nmr (Gemini, Varian) and hplc (column: adsorbosphere silica 5u, 4.6 x 250 mm; eluent: 15% ethyl acetate in hexanes; flow rate:1.5 ml/min; detection: 254 nm).



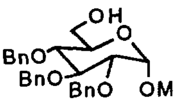
2a R' = Me; **2b** R' = Bn



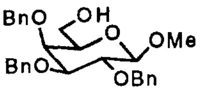
2c R' = Me; **2d** R' = Bn



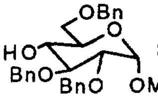
2e



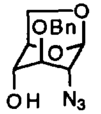
3a



3b



3c



3d

The glycosyl donors (**2**) couple with glycosyl acceptors (**3**) under a wide range of reaction conditions. For example, promoters can be Lewis acids (trimethylsilyl triflate, boron trifluoride diethyl etherate, zinc chloride, and lithium perchlorate), alkylative agents (methyl iodide/collidine), and organic salts (pyridinium or lutidinium *p*-toluenesulfonate). After screening several combinations of promoters and solvents, we observed general α-selectivity using alkylative agents and β-selectivity using strong Lewis acids. Promising protocols are lutidinium *p*-toluenesulfonate (LPTS)/*n*-Bu_4NI in benzene and trimethylsilyl triflate (TMSOTf) in propionitrile. While the two protocols afforded comparable yields, their influence on stereoselectivity was dramatically different. Under the glycosidation conditions of LPTS/Bu_4NI in benzene at 40 °C (method A), 1,2-*cis* glycosides were obtained as the major products from glucosyl and galactosyl donors, whereas 1,2-*trans* glycosides were formed predominantly in the presence of TMSOTf (method B).[8]

In general, good α- (entries 1-5) and β-selectivity (entries 6-11) were observed for the primary acceptor alcohols (**3a-b**) and the ratios decrease with secondary or hindered glycosyl acceptors (entries 12-13). As anticipated, α-selectivity was found in the glycosidation of mannosyl donor (**2e**) with acceptors (entries 14-16). The coupling of (**2e**) with hindered glycosyl acceptors such as (**3d**) gave only α-isomers (entry 16). This trend is attributed to the axial 2-*O*-benzyl group which inhibits the attack of acceptor alcohols from the β face, consequently leading to a high α-selectivity. It is interesting to note that the azide group in (**3d**) survives well during glycosidation with glycosyl phosporimidate under these conditions, as opposed to when glycosyl diethyl phosphite was used as a glycosyl donor.

Glycopyranosyl *N*-phenyl phosphorimidates, prepared by the Staudinger reaction, have been found to effect either 1,2-*cis* or 1,2-*trans* glycosidation selectively under different reaction conditions. The use of the Staudinger reaction can potentially provide a convenient method to form a library of the desired glycosyl phosphorimidates by modifying the substituents on phosphorus. Although the high levels of stereoselectivity (α or β) with tested phosphorimidates were observed only in select cases, the results from this class of the new pentavalent phosphorus derivatives are sufficiently encouraging to warrant future modification of the substituents on the phosphorus leaving groups in achieving selective glycosidation across varied substrates.

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6. Selected data of ^{1}H (200 MHz, $CDCl_3$) NMR: **2a**: δ 5.92 (dd, J = 3.3 Hz, J_{HP} = 7.8 Hz, 1H, α), 5.01 (t, J = J_{HP} = 7.6 Hz, 1H, β). **2b**: δ 6.15 (dd, J = 3.2 Hz, J_{HP} = 7.7 Hz, 1H, α). **2c**: δ 5.99 (dd, J = 3.2 Hz, J_{HP} = 7.7 Hz, 1H, α), 5.04 (t, J = J_{HP} = 7.8 Hz, 1H, β). **2d**: δ 6.12 (dd, J = 3.5 Hz, J_{HP} = 7.7 Hz, 1H, α), 5.27 (t, J = J_{HP} = 7.8 Hz, 1H, β). **2e**: δ 5,83 (dd, J = 2.0 Hz, J_{HP} = 7.7 Hz, 1H, β). **4**: δ 5.23 (d, J = 3.8 Hz, 1H, α), 4.23 (d, J = 7.5 Hz, 1H, β). **6**: δ 5.04 (d, J = 3.3 Hz, 1H, α), 4.23 (d, J = 7.6 Hz, 1H, β). **8**: δ 4.81 (d, J = 3.6 Hz, 1H, α), 4.27 (d, J = 7.4 Hz, 1H, β). **9**: δ 4.26 (d, J = 7.6 Hz, 1H, β). **10**: δ 5.75 (d, J = 3.7 Hz, 1H, α), 4.28 (d, J = 7.6 Hz, 1H, β).
7. Selected data of ^{13}C (50 MHz, $CDCl_3$) NMR: **2a**: δ 95.0 (d, J_{CP} = 8.4, C-1, α), 98.9 (d, J_{CP} = 7.5 Hz, C-1, β). **2b**: δ 95.7 (d, J_{CP} = 8.8 Hz, C-1, α). **2d**: δ 96.7 (d, J_{CP} = 8.5 Hz, C-1, α), 99.6 (d, J_{CP} = 8.4 Hz, C-1, β). **4**: δ 98.5 (C-1', α), 104.0 (C-1', β). **6**: δ 98.4 (C-1', α), 104.4 (C-1', β). **8**: δ 97.3 (C-1', α), 104.0 (C-1', β), 105.5 (C-1, β). **9**: δ 104.2 (C-1', β), 105.5 (C-1, β). **10**: δ 98.1 (C-1', α), 98.3 (C-1, α), 103.7 (C-1', β).
8. There has been considerable debate as to the exact mechanism of the formation of either 1,2-*trans* or 1,2-*cis* glycosides. Consequently, they can be assumed to result from coupling of glycosyl acceptors with the corresponding α- or β-ion-pair intermediates, respectively. For the discussion of the anomeric effect, see: Juaristi, E.; Cuevas, G. *Tetrahedron* **1992**, *48*, 5019.

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