# Electrochemical Glycosylation using Phenyl *S*-Glycosides

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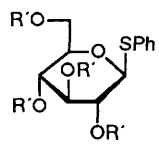
Phenyl *S*-glycosides react with alcohols under mild electrochemical conditions in a divided cell to give the corresponding *O*-glycosides.

*S*-Glycosides have recently attracted considerable attention as glycosyl donors[1] owing to their stability under a variety of chemical transformations and their regioselective activation by various thiophilic reagents.[1,2] Toxicity, difficulty in handling, and/or the high cost associated with most promoters reported up to now, may well be a serious limitation to large scale synthesis. Here we disclose that phenyl *S*-glycosides can also be transformed into *O*-glycosides under mild electrochemical conditions:

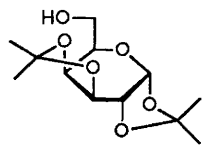
$$\text{Gly–SPh} + \text{ROH} \rightarrow \text{Gly–OR} + 1/2\ \text{PhSSPh} + \text{H}^+ + \text{e}^- \quad (1)$$

It is known[3] that alkyl phenyl sulphides (Ph–S–R) are easily oxidized[4] anodically to provide a radical cation $(\text{Ph–S–R})^{+\cdot}$ which may undergo S–R bond cleavage to give a thiyl radical ($\text{PhS}^\cdot$) and a cation ($\text{R}^+$). Such a reaction pathway is controlled by the stability of ($\text{R}^+$), and therefore should be particularly favoured in the case of glycosyl phenyl sulphides (Gly–SPh), since glycosyl cations are stabilized by the neighbouring oxygen atom. Then they may undergo nucleophilic attack by an alcohol to afford eventually an *O*-glycoside:

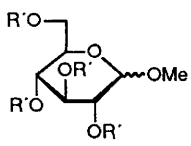
$$\text{Gly–SPh} \rightarrow \text{Gly–SPh}^{+\cdot} + \text{e}^- \quad (2)$$
$$\text{Gly–SPh}^{+\cdot} \rightarrow \text{Gly}^+ + \text{PhS}^\cdot \quad (3)$$
$$2\,\text{PhS}^\cdot \rightarrow \text{PhSSPh} \quad (4)$$
$$\text{Gly}^+ + \text{ROH} \rightarrow \text{Gly–OR} + \text{H}^+ \quad (5)$$



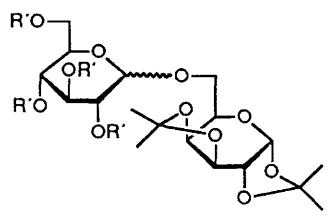

(1); R'= Bn
(2); R'=Ac




(3)




(4)(α or β); R'= Bn
(6)(α or β); R'= Ac




(5)(α or β); R'= Bn
(7)(α or β); R'= Ac

Bn = $PhCH_2$

**Table 1.** Electrochemical glycosylation.[a]

| Entry | Substrate | ROH | F mol$^{-1}$[b] | Product | α:β[c] | Yield[d]/% |
|---|---|---|---|---|---|---|
| 1 | (**1**)[5] | MeOH | 1.5 | (**4**)[6] | 1:3 | 84 |
| 2 | (**1**) | (**3**)[7] | 1.9 | (**5**)[8] | 1:4 | 63 |
| 3 | (**2**)[9] | MeOH | 2.3 | (**6**)[10] | 0:1 | 50 |
| 4 | (**2**) | (**3**) | 1.1 | (**7**)[11] | 0:1 | 50 |

[a] The oxidation potential of both reactants (**1**) and (**2**) was +1.8 V *vs.* standard calomel electrode (SCE) as determined in acetonitrile by cyclic voltammetry at a carbon electrode (scan rate of 200 mV s$^{-1}$).† See Scheme 1 for designation of substrates, alcohols, and products. [b] Faraday per mole of (**1**) or (**2**). [c] The α:β ratio was determined by $^1$H NMR spectroscopy. [d] Isolated yield (not optimized).

The reaction was first tested with methanol as a model nucleophile and applied successfully to 1,2:3,4-di-*O*-isopropylidene-α-D-galactose (see Table 1).

The electrolyses were carried out at room temperature under nitrogen in a divided cell equiped with a woven carbon anode and a platinum gauze cathode. Phenyl *S*-glucoside (1.2 mmol), alcoholic nucleophile (1.4 mmol), and dried potassium carbonate (1.2 mmol) were introduced into the anodic compartment (30 ml of dried acetonitrile containing 0.1 M $Bu^n_4NBF_4$ as the supporting electrolyte). The electrolyses were performed at a constant current until complete disappearance of the phenyl *S*-glucoside which was monitored by HPLC and TLC. After acetonitrile evaporation and treatment with water, the residue was extracted with ether. After flash chromatography, pure *O*-glucosides showed spectroscopic data ($^1$H NMR, $^{13}$C NMR, and mass spectra) in agreement with the literature.

The reaction of phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (**2**) gave only β-*O*-glucosides owing to a 1,2-*trans* effect (Table 1, entries 3 and 4). Phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**1**) bearing a 'non participating' protective group afforded mixtures of the α- and β-anomers. The β-stereoselectivities obtained by this method (entries 1 and 2) are in agreement with usual results[1] as soon as one assumes the involvement of an α-nitrilium kinetic intermediate formed by acetonitrile trapping of the cation generated in reaction (**3**).[12]

This present electro-oxidative glycosylation amounts to an economical generation of the reactive oxycarbenium species from a phenyl *S*-glycoside and is complementary to existing chemical activation procedures. By comparison to a previous report by Noyori[13] based on the use of aryl *O*-glycosides, the present method has the advantages of requiring easily available starting materials and lower oxidation potentials. This latter fact makes this electroglycosylation particularly attractive with respect to compatibility with various protecting groups which could otherwise be oxidized at larger potential.[13,14]

The scope of this strategy is now under investigation.

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† The diphenyl disulphide (PhSSPh) produced in reaction (4) is also partially oxidized ($E^p$ ~+1.8 V at 200 mV s$^{-1}$ *vs.* SCE, for previous report see *e.g.*, A. Bewick, D. E. Coe, J. M. Mellor, and D. J. Walton, *J. Chem. Soc., Chem. Commun.*, 1980, 52) which is the reason for an electron consumption larger than 1 F mol$^{-1}$. PhSSPh was identified by mass spectroscopy and by comparison with an authentic sample by HPLC and TLC.

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