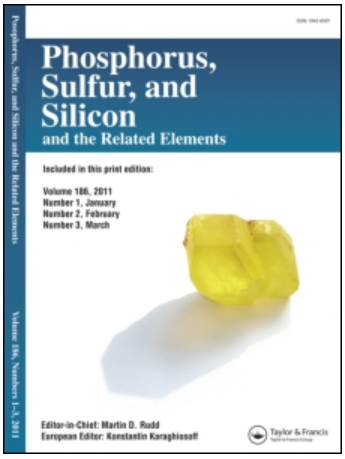

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A Novel and Facile Route to the Phosphorylation of Carbohydrates by The S-L PTC Modified Procedure of the Atherton-Todd Reaction

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A NOVEL AND FACILE ROUTE TO THE PHOSPHORYLATION OF CARBOHYDRATES BY THE S-L PTC MODIFIED PROCEDURE OF THE ATHERTON-TODD REACTION

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The various phosphates of mono- and diols of carbohydrates have been conveniently prepared in good yield by the S-L PTC modified procedure of the Atherton-Todd reaction.

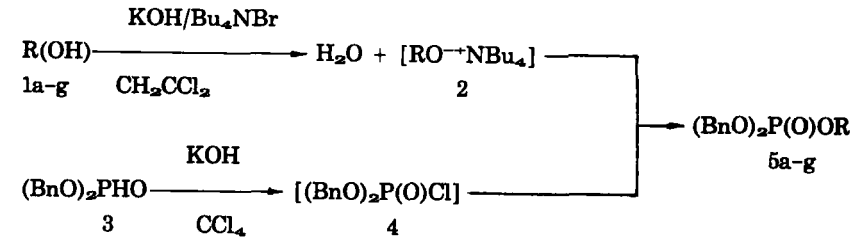
Key words: Phosphorylation, carbohydrate phosphates, phase-transfer catalysis, Atherton-Todd reaction.

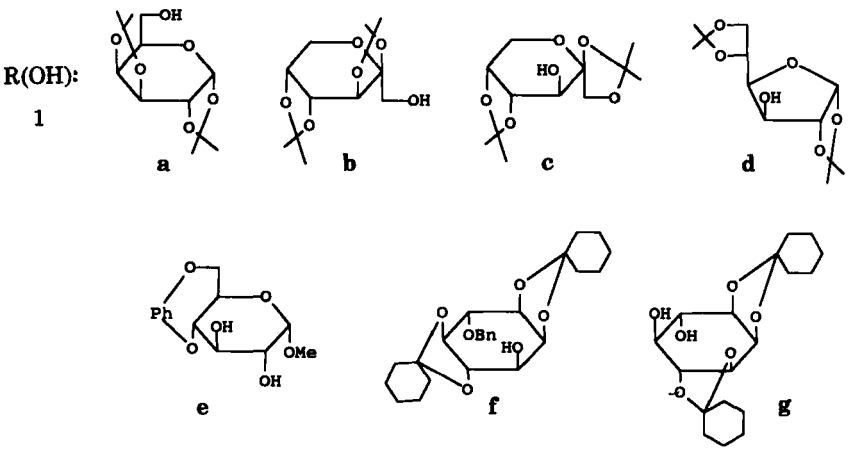
The carbohydrate phosphates perform a dominant role in living system. They serve as intermediates of metabolisms and also function as substrates in some biological processes. More importantly, carbohydrate phosphates occur as constituents of nucleic acids and coenzymes.

In order to study the functions and properties of these phosphorylated species, many efficient synthetic methods not only of the naturally occurring molecules, but also of analogs have been developed. Some excellent reviews on phosphorylation methods have appeared in the literature.[1] On the other hand, phosphorylation of alcohols by the Atherton-Todd reaction[2] is a convenient method. The L-L PTC version of this reaction is apparently more convenient and versatile.[3] However the preparative usefulness of this procedure is also limited to primary alcohols and lower dialkyl phosphonates as phosphorylating agents. Secondary and tertiary alcohols, probably due to steric hindrance, exhibit much lower reactivity and give very low yield. For this reason the Atherton-Todd reaction has not been used for the phosphorylation of hydroxyl groups in biomolecules so far.

It is a purpose of this work to show that the S-L phase-transfer catalysis (KOH/CH_2Cl_2—CCl_4/Bu_4NBr) modified procedure of the Atherton-Todd reaction is particularly useful for the phosphorylation of carbohydrates.

This modified procedure made full use of advantages of the S-L PTC method. We believe that the ion pair (**2**) of oxygen anion of carbohydrate/tetrabutylammonium cation formed under S-L PTC condition attacked the dialkyl phosphoryl chloride (**4**), intermediate of the Atherton-Todd reaction,[4] to give the product carbohydrate phosphate in the last step of the reaction. The successes of the novel method are attributed to the higher reactivity of oxygen anion of carbohydrate and the lower concentration of free hydroxide ion which can result in some side reaction under reaction condition. The formation of the intermediate, dialkyl phosphoryl chloride, can be envisaged, which underwent very slow decomposition under the S-L PTC condition in comparison with L-L PTC. We did not find the partial dealkylation of the phosphite that occurred in L-L PTC procedure.[3] The KOH had





three functions in this reaction: it captured the proton of hydroxyl group of carbohydrate; it binded water; it reacted with tetrachloromethane and dialkyl phosphonate to offer dialkyl phosphoryl chloride.

The novel procedure has some advantages over other synthetic routes. The reaction condition was mild and easy to operate. The reaction was carried out at room temperature and below it, above 25°C the side reaction became obvious. This procedure did not require anhydrous solvents; it employed the cheapest and readily available phosphorylation agent which is neutral, stable and convenient to handle. The mixed solvent of CH_2Cl_2 (or CH_3CN) and CCl_4 was used satisfactorily, CH_2Cl_2 may increase the solubility of carbohydrate and dilute the concentration of CCl_4; sole use of CCl_4 as solvent will result in a higher concentration of the intermediate and more serious side reaction. It is worth emphasizing that all compounds prepared by this method were formed in good yield. The use of an excess of phosphorylating agent favours the increase of yield. Dimethyl phosphonate (**6**) has same reactivity as dibenzyl phosphonate (**3**).

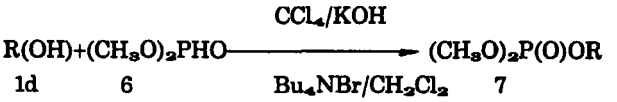


TABLE I
The phosphorylation of carbohydrates

Eutry	Products	reaction temperature ℃	reaction time	m.p. ℃	isolated yield %
1	5a	r.t	1	oil	95
2	5b	r.t	2	oil	75
3	5c	10	5	oil	70
4	5d	r.t	4	39–40	81
5	5e	r.t	3	95–96	90
6	5f	10	3	oil	84
7	5g	r.t	6	oil	85
8	7	r.t	5	78–79	83

The wide utility of the recommended phosphorylation procedure has been proven on a relatively representative spectrum of carbohydrates presented in Table I. In order to expand the scope of the method the examination of the reaction with other compounds with P—H bond is in progress.

In conclusion, in this paper we have demonstrated that the S-L PTC modified procedure of the Atherton-Todd reaction is a novel and effective method for the phosphorylation of carbohydrates. The advantages of this procedure are good yields, the short reaction time and ease with which the reaction can be carried out at room temperature with readily available materials. Due to the important biological activity of this class of compounds, the described procedure should find wide application in the synthesis of carbohydrate phosphates and its analogues.

EXPERIMENTAL

Microanalyses were performed on a RaPid CHN—O—S analyser. Mass spectra were run on a Finnigan-MATB430 spectrometer. ^1H and ^{31}P NMR spectra were recorded on a AMX-300 (300 MHZ) instrument in $CDCl_3$ with TMS as internal standard and 85% H_3PO_4 as external standard, respectively. Melting points were uncorrected.

Reagent grade solvents were used directly without treatment. Dibenzyl phosphonate and dimethyl phosphonate were prepared from alcohol and phosphorus trichloride.[5] Carbohydrates were protected according to references methods.[6–11] TLC was performed with commercial silica gel plates (GF254), visualization was done with UV light or by dipping the plate into a solution of phenol (**3g**)/sulfuric acid (5 mL)/EtOH (95 mL) followed by heating.

The general procedure for phosphorylation of carbohydrates: To a stirred mixture of carbohydrate derivative (1 mmol), tetra-*n*-butylammonium bromide (0.2–0.5 mmol) and powdered KOH (10 mmol) in a mixed solvent (10 mL) of dichloromethane-tetrachloromethane (1:0.2) was slowly added the solution of dibenzyl phosphonate (1.1–2.0 equiv.) in CH_2Cl_2 (1 mL) at 10–15°C. The progress of the reaction was monitored by TLC. After the reaction was completed (about 0.5–4 hr), the mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel to afford pure carbohydrate phosphate.

1,2,3,4,-Di-o-iospropylidene-α-D-galacopyranose-6-dibenzylphosphate (**5a**)

eluent: ethyl acetate/petroleum, 1:1, R_f = 0.60.
^1H NMR: δ = 1.30, 1.31, 1.41, 1.49 (4s, 3H each), 4.02–4.07 (m, 1H), 4.11–4.20 (m, 3H), 4.32 (dd,

1H), 4.59 (dd, 1H), 5.06, 5.07 (2d, 2H each, $^3J_{P-H}$ = 7.7 Hz), 5.52 (d, 1H), 7.36 (m, 10H).
^{31}P NMR: −0.41.
MS(EI): m/z(%) = 521 (M + 1, 0.95), 447 (1.7), 279 (10.44), 207 (19.62), 149 (10.54), 99 (27.84), 91 (100).
$C_{26}H_{33}O_9P$ (520.49) calc: C 59.99; H 6.39. found: C 59.72; H 6.67.

2,3,4,5-Di-o-isopropylidene-β-D-fructopyranose-1-dibenzylphosphate (**5b**)

eluent: chloroform/ether acetate, 7:1, R_f = 0.41.
^{1}H NMR: δ = 1.31, 1.34, 1.40, 1.51 (4s, 3H each), 3.77 (d, 1H), 3.89 (dd, 1H), 4.10 (m, 2H), 4.20 (m, 1H), 4.32 (dd, 1H), 4.57 (dd, 1H), 5.06, 5.07 (2d, 2H each, $^3J_{P-H}$ = 7.7 Hz), 7.31 (m, 10H).
^{31}P NMR: δ = −0.85.
MS(FAB): m/z(%) = 521 (M + 1, 20.1), 267 (7.8), 181 (8.1), 91 (100).
$C_{26}H_{33}O_9P$ (520.49) calc: C 59.99; H 6.39. found: C 59.75; H 6.15.

1,2,4,5-Di-o-isopropylidene-β-D-fructopyranose-3-dibenzylphosphate (**5c**)

eluent: ethyl acetate/petroleum, 1:1, R_f = 0.64.
^{1}H NMR: δ = 1.36, 1.40, 1.50, 1.53 (4s, 3H each), 3.99 (d, 1H), 4.09 (s, 1H), 4.13 (d, 1H), 4.23 (dd, 1H), 4.35 (m, 2H), 4.53 (dd, 1H), 5.10, 5.15 (2d, 2H each, $^3J_{P-H}$ = 7.7 Hz), 7.3 (m, 10H).
^{31}P NMR: δ = −1.21.
MS(FAB): m/z(%) = 521 (M + 1, 4.0), 279 (20.1), 181 (11.7), 91 (100).
$C_{26}H_{33}O_9P$ (520.49) calc: C 59.99; H 6.39. found: C 59.81; H 6.54.

1,2,5,6-Di-o-isopropylidene-α-D-glucofuranose-3-dibenzylphosphate (**5d**)

eluent: ethyl acetate/petroleum, 4:6, R_f = 0.61.
^{1}H NMR: δ = 1.25 (s, 6H), 1.37, 1.47 (2s, 3H each), 3.94–4.13 (m, 3H), 4.20–4.27 (m, 1H), 4.60 (d, 1H), 4.83 (dd, 1H), 5.10, 5.11 (2d, 2H each, $^3J_{P-H}$ = 7.7 Hz), 5.76 (d, 1H), 7.35 (m, 10H).
^{31}P NMR: δ = −1.28.
MS(FAB): m/z(%) = 521 (M + 1, 6.0), 505 (4.0), 463 (9.4), 267 (27.1), 99 (37.2), 91 (100).
$C_{26}H_{33}O_9P$ (520.49) calc: C 59.99; H 6.39. found: C 59.75; H 6.42.

Methyl-4,6-benzylidene-α-D-glucopyronoside-2,3-bis(dibenzylphosphate) (**5e**)

eluent: ethyl acetate/petroleum, 1:1 R_f = 0.35.
^{1}H NMR: δ = 3.35 (s, 3H), 3.64 (t, 1H), 3.74 (t, 1H), 3.92 (m, 1H), 4.29 (dd, 1H), 4.43 (m, 1H), 4.80–5.08 (m, 9H), 5.10 (d, 1H), 5.49 (s, 1H), 5.49 (s, 1H), 6.98–7.50 (m, 25H).
^{31}P NMR: δ = −1.15, −1.50.
MS(FAB): m/z(%) = 803 (M + 1, 36.7), 713(4.8), 181(17.5), 105(13.6), 91(100).
$C_{42}H_{44}O_{12}P_2$ (802.71) calc: C 62.84; H 5.53. found: C 62.64; H 5.62.

1,2,4,5-Di-o-cyclohexylidene-6-o-benzyl-myo-inositol-3-dibenzylphosphate (**5f**)

eluent: ethyl acetate/petroleum, 1:1, R_f = 0.38.
^{1} NMR: δ = 1.35–1.74 (m, 20H), 3.44 (dd, 1H), 3.67 (dd 1H), 4.04 (dd, 1H), 4.15 (t, 1H), 4.57 (dd, 1H), 4.76 (dd, 1H), 4.86 (s, 2H), 5.12, 5.17 (2d, 2H each, $^3J_{P-H}$ = 7.7 Hz), 7.30–7.47 (m, 15H).
^{31}P NMR: δ = −1.51.
MS(EI): m/z(%) = 691 (M + 1, 2.27), 486(4.31), 298(4.02), 279(4.78), 201(2.56), 91(100).
$C_{39}H_{47}O_9P$ (690.74) calc: C 67.81; H 6.86. found: C 67.75; H 6.81.

1,2,3,4-Di-o-cyclohexylidene-myo-inositol-5,6-bis(dibenzylphosphate) (**5g**)

eluent: ethyl acetate/petroleum, 4:6, R_f = 0.79.
^{1}H NMR: δ = 1.26–1.80 (m, 20H), 3.63 (dd, 1H), 4.17 (dd, 1H), 4.40 (m, 1H), 4.46 (dd, 1H), 4.74–4.86 (m, 2H), 4.96–5.12 (m, 8H), 7.24–7.37 (m, 20H).
^{31}P NMR: δ = −1.93, −1.80.
MS(FAB): m/z(%) = 861 (M + 1, 5.24), 771 (1.77), 207 (1.84), 181(6.80), 91(100).
$C_{46}H_{54}O_{12}P_2$ (860.83) calc: C 64.18; H 6.32. found: C 64.11; H 6.25.

1,2,5,6-Di-o-isopropylidene-α-D-glucofuranose-3-dimethylphosphate (**7**)

eluent: ethyl acetate/petroleum, 6:4, R_f = 0.33.
^{1}H NMR: δ = 1.32, 1.33, 1.43, 1.50 (4s, 3H each), 3.81, 3.83 (2d, 3H each, $^3J_{P-H}$ = 11 Hz), 4.0 (dd, 1H), 4.1–4.15 (m, 2H), 4.23–4.32 (m, 1H), 4.73–4.85 (m, 2H), 5.91 (d, 1H).
^{31}P NMR: δ = 1.014.

MS(FAB): m/z(%) = 369 (M + 1, 24), 353 (33.8), 311 (52.0), 253(31.5), 127(100), 101(31.1). $C_{14}H_{25}O_9P$ (368.31) calc: C 45.64; H 6.84. found: C 45.37; H 7.07.

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