Oxyphosphorylation of Carbon with Phosphoric Acid and *p*-(Difluoroiodo)toluene: Synthesis of Tris-ketol Phosphates and their Conversion into Lithium Bis-ketol Phosphates

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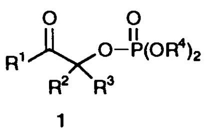
The synthesis of tris-ketol phosphates by the treatment of phosphoric acid–*p*-(difluoroiodo)toluene mixtures with silyl enol ethers and their conversion into lithium bis-ketol phosphates by the action of lithium bromide in acetone are described.

Mono-ketol phosphates **1** have long attracted interest as sugar analogues,[1] and, because the selective hydrolytic removal of the ketoxide ligand can be achieved under mildly basic conditions,[2] they have been employed as intermediates in phospholipid and oligonucleotide synthesis (*i.e.*, when $R^1 = R^2 = Me, R^3 = H$).[3] More recently, their mechanism of alkaline hydrolysis has been proposed as a model for the ATP-mediated enzymic carboxylation of biotin.[2c] The rapid photorelease of cAMP from benzoin-protected cAMP, a caged mono-ketol nucleotide, has also been reported.[4]

In contrast to **1**, bis- and tris-ketol phosphates, **2** and **3**, have not, to our knowledge, been described. We have applied hypervalent iodine methodology to this problem[5] and now report that phosphoric acid, when employed in conjunction with *p*-(difluoroiodo)toluene (**4**; DFIT),[6,7] can be exhaustively functionalized with silyl enol ethers (SEEs) to give tris-ketol phosphates (Scheme 1). The tris-ketol phosphates can be used, in turn, for the synthesis of lithium bis-ketol phosphates.



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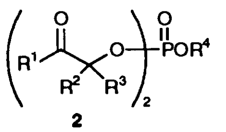

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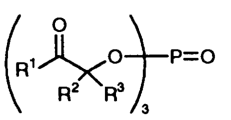

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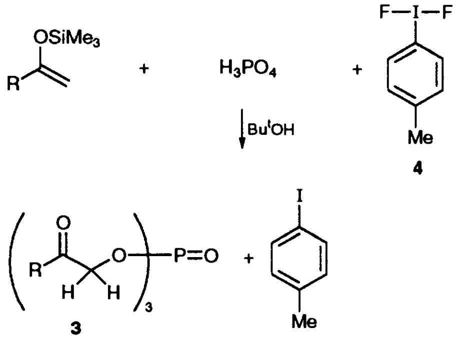
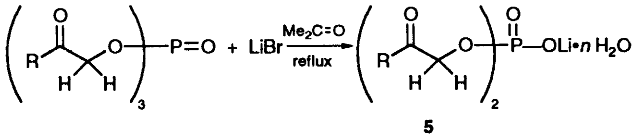
In a typical experiment, a mixture of crystalline anhydrous H_3PO_4 (1.02 mmol) and DFIT (3.05 mmol) in dry *tert*-butyl alcohol (15 cm³) was treated, under N_2, with the SEE of acetophenone (6.5 mmol, room temp.). After 5.75 h, the mixture was concentrated, and the residual semi-solid was recrystallized from acetone–hexanes to give the tris-ketol phosphate **3a** (62.5%). Similar treatment of DFIT–H_3PO_4 mixtures with the SEEs of acetone, pinacolone, 2-acetylpyridine and 2-acetylfuran gave the tris-ketol phosphates **3b–e** in yields in the range 60–73%.

The starting molar ratios of DFIT to H_3PO_4 for the reactions shown in Scheme 1 were deliberately adjusted to 3 : 1, and it might be expected that 2 : 1 and 1 : 1 molar ratios should permit stoichiometrically controlled syntheses of bis-ketol hydrogen and mono-ketol dihydrogen phosphates. However, when the SEE of aceptophenone was added to a 1 : 1 molar mixture (*i.e.*, 2.0 mmol each) of DFIT and H_3PO_4 in *tert*-butyl alcohol, oxyphosphorylation still proceeded primarily to the tris-ketol phosphate stage, and **3a** was isolated in 51% yield. The mono-ketol dihydrogen phosphate was tentatively identified (¹H NMR) among the by-products, but the yield was low and this material was not purified.



Scheme 1

	R	Yield (%)
3a	Ph	62.5
3b	Me	64
3c	Bu^t	73
3d	2-Pyridyl	60
3e	2-Furyl	60



Scheme 2

	R	*n*	Yield (%)
5a	Ph	0.5	89
5b	Me	0.5	79
5c	Bu^t	0.5	84
5d	2-Pyridyl	0	83
5e	2-Furyl	1	91

The availability of **3a–e** from phosphoric acid prompted us to explore their utility as precursors to bis-ketol phosphates. The tris-ketol phosphates (scale range *ca.* 0.19–1.1 mmol) when allowed to react with lithium bromide in acetone (reflux, N_2) gave the corresponding lithium bis-ketol phosphates **5a–e** in 79–91% yields (Scheme 2). This is an operationally convenient procedure, since the lithium bis-ketol phosphates separate from acetone as they are produced.

Because the hydrogen and carbon nuclei are somewhat deshielded and coupled with phosphorus, the (C=O)CH₂–O–P linkages of ketol phosphates afford especially diagnostic NMR spectra. The ¹H (300 MHz) and ¹³C resonances of **3a–e** and **5a–e** appear as relatively lowfield doublets, while the ¹H-coupled ³¹P resonances clearly reveal the number of ketoxide ligands bound to phosphorus. Thus, while mono-ketol phosphates of

Table 1 Selected NMR data for tris-ketol phosphates and lithium bis-ketol phosphates[a]

Ketol phosphate	NMR[b]		
	$^1H(\delta,J_{HP})$	$^{13}C(\delta,J_{CP})$	$^{31}P(\delta,J_{PH})$
3a[c]	5.58, 11.1	69.6, 5.6; 192.3, 4.7	0.0, 11.1
3b[d]	4.70, 11.0	71.25, 5.9; 201.6, 4.9	−1.0, 11.0
3c[e]	5.02, 11.0	67.8, 5.8; 207.9, 3.8	−0.3, 10.9
3d	5.84, 10.9	70.3, 5.4; 193.3, 5.0	+0.3, 10.9
3e	5.38, 11.3	68.8, 5.2; 181.6, 4.8	−0.0(5), 11.3
5a$\cdot 0.5H_2O$	5.04, 7.6	67.9, 5.0; 195.8, 7.3	−1.1, 7.6
5b$\cdot 0.5H_2O$	4.22, 8.5	69.9, 5.1; 206.8, 9.8	−1.1, 8.5
5c$\cdot 0.5H_2O$	4.56, 7.1	65.6, 4.8; 210.5, 6.9	−1.1, 6.8
5d[e]	5.31, 7.5	67.8, 4.7; 196.15, 6.7	−0.8, 7.4
5e$\cdot H_2O$[e]	4.79, 8.0	67.2, 5.1; 184.75, 7.0	−1.1, 7.9

[a] The C, H analyses were within ±0.3% for all ketol phosphates except **5c**$\cdot 1/2\ H_2O$ ($\Delta C = +0.34\%$) and **3b**. The ^1H NMR spectrum and C, H analysis (±0.3%) of **3b** indicated the presence of 11.8 mole % of $(MeCOCH_2O)_2PO_2H$ in the analytical sample. [b] **3a**–**3e** ($CDCl_3$), **5a**–**5e** ([$^2H_6$]DMSO); ^{31}P chemical shifts are referenced to 85% H_3PO_4 (sealed capillary); coupling constants are given in Hz. [c] The analytical (C, H) and ^{13}C NMR data for **3a** were obtained on a sample of **3a** prepared from an isolated iodine(III)–phosphate reagent and the SEE of acetophenone in CH_2Cl_2. The iodine(III)-phosphate was made from $PhI(OAc)_2$ and anhydrous H_3PO_4 in dry MeCN. [d] The NMR spectra for **3b** were obtained on clean sample of **3b** prepared by the treatment of DFIT and anhydrous H_3PO_4 with acetone. [e] Minor impurities detected by NMR analysis.

general structure $RCOCH_2OP(O)(OPh)_2$ give rise to a triplet due to the coupling of phosphorus with two α-hydrogens,[5c] the ^{31}P spectra of the lithium bis-ketol phosphates exhibit a quintet (four α-hydrogens), and the spectra of the tris-ketol phosphates show a septet (six α-hydrogens). Selected NMR data are given in Table 1.

In summary, the synthesis of the first examples of tris-ketol phosphates and bis-ketol phosphates (isolated as their lithium salts) is reported. Application of the hypervalent iodine-exhaustive ketolization methodology to pyrophosphoric acid and the use of tetrakis-ketol pyrophosphates and bis-ketol hydrogen phosphates for the synthesis of bis-ketol phosphate derivatives of AZT will be reported later.

Acknowledgements

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