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REGIOSPECIFIC CONVERSION OF TERMINAL ALKYNES TO KETOL PHOSPHATES WITH AN IODINE(III)-PHOSPHATE REAGENT

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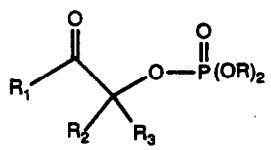
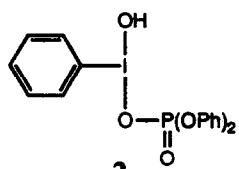
Abstract: Terminal alkynes undergo regiospecific conversion to ketol phosphates when treated with the iodine(III)-phosphate 2 in acetonitrile containing water.

The oxyphosphorylation of carbon with hypervalent iodine compounds is a promising new approach to phosphate esters.[1,2] Of particular interest here is a recent study of the direct conversion of ketones to ketol phosphates 1 (R = Ph) with the iodine(III)-phosphate 2.[2] Ketol phosphates have engendered interest as sugar analogs[3] and as intermediates in phospholipid and nucleotide synthesis.[4] They are exceptionally reactive toward alkaline hydrolysis,[5,6] the mechanism of which has been posited as a model for the ATP-mediated enzymic carboxylation of biotin.[6] Although the direct synthesis of ketol phosphates from ketones with 2 affords some advantage over methods requiring either α-hydroxyketones[6] or trialkoxydioxaphospholenes[3,7] as starting materials, it is not regiospecific. Thus, when 2-hexanone was treated with 2, a 1.3:1.0 mixture of the 1- and 3-diphenyl phosphate derivatives was obtained.[8]

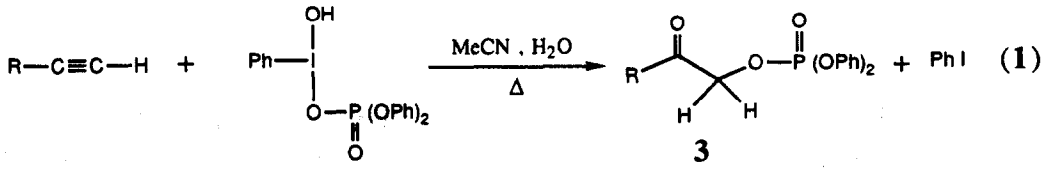


1



2

We now report that terminal alkynes react regiospecifically with 2 in acetonitrile spiked with H_2O to give ketol phosphates of general structure 3; eq 1. In a typical experiment, a mixture of 1-heptyne (20 mmol), 2 (5.00 mmol) and H_2O (10 mmol) in MeCN (50 mL) was heated under reflux (2 h) and concentrated. The residual material (in CH_2Cl_2) was treated with 5% $NaHCO_3$ and H_2O, and the oil that remained was chromatographed on silica gel [hexanes (removes PhI), hexanes: EtOAc] to give 1.66 mmol of ketol phosphate 3e (R = n-C_5H_{11}). ^1H NMR analysis of a portion of the crude oil mixed with a weighed quantity of $Cl_2CHCHCl_2$, prior to chromatographic workup, gave an estimated yield of 1.7(5) mmol of 3e. Thus, the separation of the ketol phosphate was fairly efficient. Finally, acidification and concentration of the aqueous extracts allowed the recovery of 1.6 mmol of diphenyl phosphate.



3 (1)

Similar treatment of various terminal alkynes with 2 gave the ketol phosphates shown in Table I. Compounds 3a–3f, previously unreported, were characterized by elemental (C,H within ±0.4%), IR and NMR (300 MHz ^{1}H, ^{13}C, ^{31}P) analysis. The CH_2–O–P moiety in 3 affords particularly diagnostic NMR spectra since the methylene protons and carbon are deshielded and coupled with phosphorus (Table I).

Any mechanism for ketol phosphate formation based on a 1:1:1 stoichiometric ratio of alkyne, 2 and H_2O is inconsistent with the production of diphenyl phosphate (DPP) in these reactions. Indeed, the fact that DPP and 3 are generated in nearly equal yields (in mmol, Table I) suggests that they may be derived from a common precursor. Since certain alkynes (e.g., 1-hexyne) are known to react with 4, the tosylate analog of 2, to give stable β-tosyloxyvinyliodonium tosylates 5,[9] a mechanism involving the intermedate production of β-phosphoryloxyvinyliodonium phosphates 6 deserves consideration. Thus, hydrolytic cleavage of the enol phosphate linkage in 6 to give 7 and DPP and S_n collapse of 7 with loss of PhI would give 3. That 6 can, at least, be converted to 3 has been demonstrated in a preliminary ^{1}H NMR study. When 1-pentyne was treated with a mixture of 2 and DPP in $CHCl_3$ at reflux, an oil largely comprised of 6 (R = n-Pr), 3 (R = n-Pr) and the alkynyliodonium phosphate 8 was obtained.[10] Compound 6 (R = n-Pr) is quite sensitive to moisture and has not yet been isolated in a pure state. However, when the mixture of 6, 3 and 8 (ca. 6:1:3 molar ratio) was treated with H_2O (ca. 4:1 molar excess) in CD_3CN for 2 hours at ca. 70°C, 6 was almost completely converted to 3.[11] To the extent that such a process is operative in the reactions of alkynes with 2/H_2O, the percentage yields of 3 in Table I should be doubled; i.e., two molar equivalents of 2, the limiting reagent, would ultimately be required to give one molar equivalent of 3.

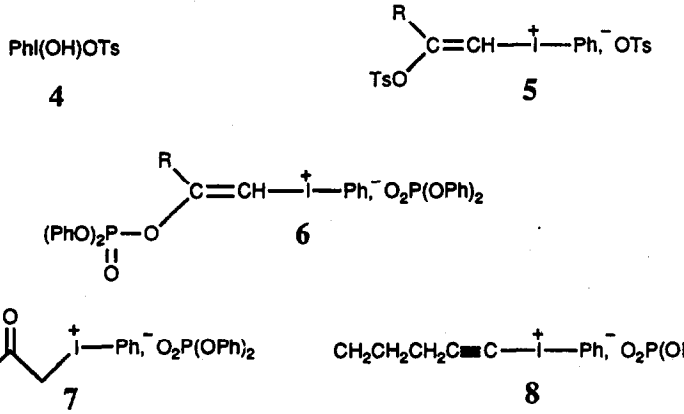
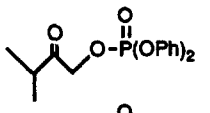
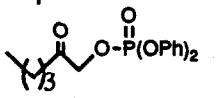
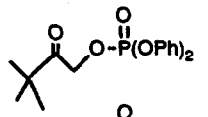
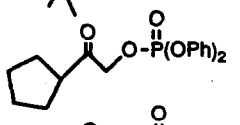
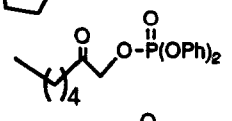
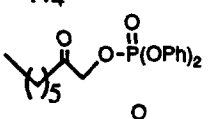
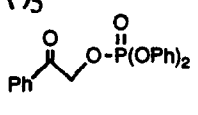


Table I. Ketol Phosphates from Terminal Alkynes with 2.[a]

	Ketol phosphate[b]	Yield(mmol, %)[d]	Yield(mmol, %) $(PhO)_2PO_2H$	NMR(δ, mult)[e] ^1H	^{13}C	^{31}P
3a		1.44, 29	1.9(6), 39	4.82, d	70.03, d	-11.7, t
3b		1.6(9), 34	1.9(6), 39	4.71, d	71.35, d	-11.9, t
3c[c]		0.86, 17	----	5.01, d	68.22, d	-11.3, t
3d		1.52, 30	1.8(0), 36	4.80, d	70.53, d	-11.8, t
3e		1.66, 33	1.6(0), 32	4.71, d	71.35, d	-11.8, t
3f		1.60, 32	1.7(6), 35	4.71, d	71.26, d	-11.8, t
3g		2.1(1), 42	----	5.43, d[f]	----	----

[a] Alkyne (20 mmol), 2(5.0 mmol), H_2O(10 mmol); less alkyne can be used. [b] **3a-3f** were isolated as oils, **3g** as a solid; all exhibited some coloration. [c] A second product, tentatively identified as $Me_3C\text{-}C{\equiv}C\text{-}OP(O)(OPh)_2$, was isolated (yellow oil, 0.247 g, 0.829 mmol). [d] Based on isolated materials which showed only minor impurities by ^1H NMR analysis (probably at least 95% pure by weight); yields with parentheses shown are based on weights determined to two significant figures. [e] ^1H NMR spectra of **3f-3f** are referenced to Me_4Si at δ 0.0, ^{13}C spectra to $CDCl_3$ at δ 77.0 and ^{31}P spectra to external 85% H_3PO_4; the J_{HP} values of **3a-3f** range from 9.1 to 10.0 Hz, J_{CP} values from 5.7 to 6.6 Hz and J_{PH} values from 9.15 to 10.0 Hz. [f] ^{13}C and ^{31}P data for **3g** are reported in reference 2.

In summary, a direct, regiospecific synthesis of ketol phosphates 3 from terminal alkynes is communicated. Issues pertaining to the stoichiometry, mechanism, optimization and scope of these reactions are slated for further investigation.

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References and Notes

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8. This work.
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10. In other experiments, both 3 (R = n-Pr, oil) and 8 (mp 99-101°C) have been isolated and characterized by NMR and elemental analysis (C,H within ±0.4%).
11. The hydrolysis of 6 (R = n-Pr to 3 (R = n-Pr) in the mixture was monitored by the disappearance of the vinyl proton resonance of 6 at δ 6.49 and the enhancement of the α-hydrogen doublet of 3 at δ 4.83 (J_{HP} = 10 Hz). Compound 8 was also consumed, but its fate has not yet been clearly established.

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