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New Organohypervalent Iodine Reagents for α-Methylphosphonylations and α-Diphenyl- and α-Dimethylphosphinylations

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Abstract: [Hydroxy(((phenoxy)(methyl)phosphoryl)oxy)iodo]benzene (**1**), [hydroxy(((diphenyl)phosphoryl)oxy)-iodo]benzene (**2**) and [hydroxy(((dimethyl)phosphoryl)oxy)iodo]benzene (**3**), obtained from the reaction of iodosobenzene with phenyl methylphosphonic acid, diphenyl- and dimethylphosphinic acid, respectively, effect the introduction of the corresponding phosphonate or phosphinate groups α- to ketone and ester carbonyl groups. Phenylacetylene is transformed by reagents **1-3** into the corresponding α-functionalized acetophenone derivatives.
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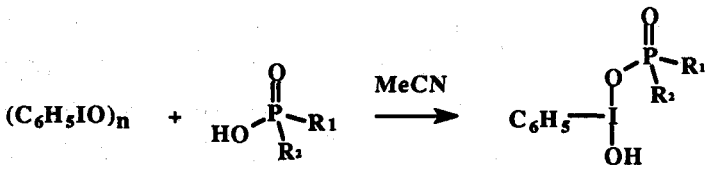
Hypervalent iodine chemistry has shown interesting applications to oxyphosphorylation of carbon in recent years as a new route to phosphate esters, in the synthesis of alkynyl phosphates from alkynyl(phenyl)iodonium phosphates,[1] in the synthesis of ketol phosphates from ketones or alkenoic acids and hypervalent iodine reagents,[2] in the synthesis of ketol phosphates from terminal alkynes and an iodine (III)-phosphate[3] and in the synthesis of bis- and tris-ketol phosphates from *p*- (difluoroiodo)toluene and silyl enol ethers.[4] Hypervalent iodine compounds have also been used as reagents for the synthesis of β-ketophosphonates.[5]

No studies of α-methylphosphonylation, α-diaryl- or α-dialkylphosphinylation of carbonyl compounds involving organohypervalent iodine reagents have been performed so far, although the method could prove useful for the formation of internucleotidic bonds in alkyl and arylphosphonate-based antisense oligonucleosides. Antisense oligonucleoside methylphosphonates have been shown to inhibit protein synthesis in both bacterial and mammalian cell-free systems and in cells in culture in a sequence-specific manner.[6] Their resistance to nuclease, sequence specific antisense activity and their ability to be taken up intact by mammalian cells makes them potential antiviral and chemotherapeutic agents.[7]

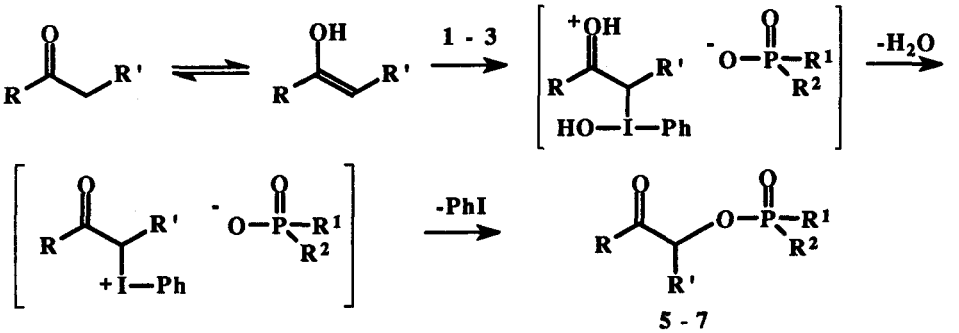
We now report the syntheses and reactions of three new organohypervalent iodine oxyphosphorylating reagents: [hydroxy(((phenoxy)(methyl)phosphoryl)oxy)iodo]benzene (**1**), [hydroxy(((diphenyl)phosphoryl)-oxy)iodo]benzene (**2**) and [hydroxy(((dimethyl)phosphoryl)oxy)iodo]benzene (**3**). The reaction of iodosobenzene with phenyl methylphosphonic acid, dimethylphosphinic acid and diphenylphosphinic acid afforded reagents **1-3** in 88-93% yields. In a typical experiment, a solution of phenylmethylphosphonic acid[8] (32 mmol) in 20 mL acetonitrile was added in one portion at room temperature to a stirred suspension of iodosobenzene (32 mmol) in 30 mL acetonitrile and the reaction mixture was stirred until almost all iodosobenzene dissolved (10 min). Insoluble material was filtered and the solution was cooled down in an ice-bath; the product crystallized out of the solution as white crystals, mp 93-95°C. A second crop was collected from the mother liquor and the total yield was 11.0 g (88%). Reagents **2** and **3**, using essentially the same procedure, required longer reaction times - 2 hours and 24 hours, respectively. Reagents **1-3** gave correct elemental analyses. The yields and spectral data for reagents **1-3** are presented in Table 1.



1 $R^1 = CH_3$, $R^2 = OC_6H_5$
2 $R^1 = R^2 = C_6H_5$
3 $R^1 = R^2 = CH_3$

Reagent **1** effects the introduction of the methylphosphonate monophenylester group -O-P(O)(CH_3)OC_6H_5 α- to the carbonyl group of ketones; this reagent also carries out α-phosphonyloxylation of β-dicarbonyl compounds such as dibenzoylmethane and ethyl acetoacetate. Typically, an equimolar mixture of **1** and ketone or ketoester in 20 mL acetonitrile is kept at reflux overnight, then concentrated *in vacuo* and subjected to flash chromatography (hexane:ethylacetate = 1:1). The yields were between 50% and 87%. In the case of acetone, acetonitrile was replaced by a large excess of acetone (70 eq.), which led to the highest yield (87%). Dibenzoylmethane reacted at room temperature. The products were characterized by ^{1}H NMR, ^{13}C NMR and ^{31}P NMR (Table 1), as well as microanalyses or high resolution mass spectroscopy.[9]

Similar to **1**, reagents **2** and **3** introduce dimethyl- and diphenylphosphinate groups α- to ketone and ester carbonyl groups. Due to their thermal stability (complete decomposition after 4 hours in refluxing acetonitrile), **2** and **3** are used at room temperature and accordingly require longer reaction times. The yields are between 19% and 48%, consistently lower than in the case of **1**. Besides their reactivity, the reagents stability seems to play an important role. The yields and spectral data for products resulting from reaction of **1-3** with various substrates are presented in Table 1. The pathway for this reaction is based on oxytosylation mechanism suggested by Koser *et al.*[10] (Scheme 1).

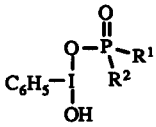
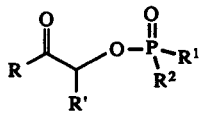
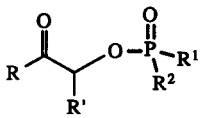


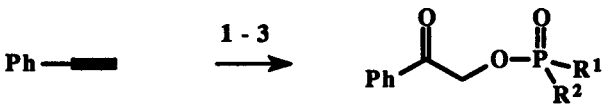
5 - 7

Scheme 1

All three new reagents **1-3** also have the ability to react with phenylacetylene[3] at room temperature to afford the corresponding α-functionalized phosphoryl ketones **5b**, **6b** or **7b**, respectively. Typically, an equimolar mixture of **1** and phenylacetylene in CH_2Cl_2 was stirred at room temperature for 16 hours; concentration *in vacuo* and flash chromatography (hexane:ethylacetate = 1:1) afforded **5b** as a clear oil.

Table 1. I(III)-Reagents 1-3, Ketol Monophenylester Methylphosphonates 5a-5e, Ketol Diphenylphosphinates 6a-6e and Ketol Dimethylphosphinates 7a-7e [12].

Compounds: Reagent(1-3) Prod.(5a-7e)	R	R'	R^1	R^2	Yield %	IR(cm^{-1}) P=O,C=O	^{1}H-NMR $\delta_{Me\text{-}P}$(mult, J_{HP}), $\delta_{CH\text{-}O\text{-}P}$(mult, J_{HP})	^{13}C-NMR $\delta_{Me\text{-}P}$(mult, J_{CP}), $\delta_{C\text{-}O\text{-}P}$(mult, J_{CP})	^{31}P-NMR δ
 Substrate 									
1	-	-	Me	OPh	88	1307, -	1.32(d,17)	11.6,13.0(2s) 120.6(d,3.9)	24.8
2	-	-	Ph	Ph	93	1308, -	7.60-8.40(m)	128(d,12.7),130 (d,11.8),131(d,10)	25.8
3	-	-	Me	Me	93	1306, -	1.25(d,13.7)	17.2,18.1(2s)	46.4
									
5a	Me	H (acetone)	Me	OPh	87	1316,1732	1.75(d,18), 4.50 and 4.72 (dd,9.1 and 17.3)	10.9,12.3(2s)	30.0
5b	Ph	H (acetophen-one)	Me	OPh	44	1314,1709	1.87(d,18), 5.25 and 5.49 (dd,8.9 and16.8)	11.2,12.6(2s), 69.7(d,6.3)	30.8
5c	-(CH_2)$_4$-	(cyclohex-anone)	Me	OPh	50	1312,1731	1.69 and 1.85 (2d, 17.7 and 18.2), 4.9(m)	11.4 and 12.8(2d, 17.4 and 18.4), 79.0 and 79.5(2d, 7.1 and 7.3)	30.2
5d	Ph	PhCO (di-Bz-methane)	Me	OPh	58	1327,1687	1.89(d,18.2)	11.3 and 12.7(2s), 80.9 and 81.5(2d)	30.6
5e	Me	CO_2Me (methylaceto-acetate)	Me	OPh	64	1316,1732	1.57 and 1.62 (2d,7.3 and 7.6), 5.21(d,9.6)	10.9 and 12.3(2s), 78.0(d,7.0)	31.5
6a	Me	H	Ph	Ph	48	1357,1739	- 4.54(d,7.9)	- 67.9(d,5.9)	34.6
6b	Ph	H	Ph	Ph	22	1230,1704	- 5.30(d,7.5)	- 65.7(d,5.0)	35.0
6c	-(CH_2)$_4$-		Ph	Ph	44	1313,1730	- 4.85(m,6.6)	- 77.4(d,6.1)	33.6
6d	Ph	PhCO	Ph	Ph	47	1280,1710	- 6.79(d,10.6)	- 79.9(d,5.9)	36.5
6e	Me	CO_2Me	Ph	Ph	32	1278,1761	- 5.26(d,10.5)	- 76.7(d,5.7)	36.7
7a	Me	H	Me	Me	47	1305,1735	1.54(d,14.1), 4.56(d,10.3)	15.1 and 17.0(2s), 67.7(d,6.3)	57.9
7b	Ph	H	Me	Me	19	1305,1703	1.63(d,14.2), 5.32(d,10.7)	15.9 and 16.9(2s), 65.6(d,6.2)	58.2
7c	-(CH_2)$_4$-		Me	Me	-	1300,1729	1.42(d,14.2), 4.87(m,10.6)	16.3 and 17.3(2s), 76.7(d,7.7)	55.0
7d	Ph	PhCO	Me	Me	45	1299,1700	1.60(d,14.1), 6.89(d,10.5)	16.6 and 17.6(2s), 78.2(d,6.8)	59.9
7e	Me	CO_2Me	Me	Me	8	1302,1738	1.60(d,14.1), 5.33(d,10.5)	16.3 and 17.3(2s), 66.2(d,6.5)	61.5



5b(27%), 6b(50%), 7b(25%)

We found that if the molar ratio **1** : phenylacetylene is doubled the yield remains almost unchanged. Based on this observation, we propose a reaction mechanism that involves **8** rather than **9** as intermediate.

8 **9**

Finally, the totality of these results conforms to a pattern of reaction type originally found for Koser's reagent in which the group OTs of the reagent PhI(OH)OTs[11] is formally introduced as $^{+}$OTs α to a carbonyl group in a umpolung sense. Accordingly, the reagents of this paper provide synthetic equivalents which may be thought of as $^{+}$O-P(O)(CH_3)OC_6H_5 (from **1**), $^{+}$O-P(O)(C_6H_5)$_2$ (from **2**) and $^{+}$O-P(O)(CH_3)$_2$ (from **3**).

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[#] On leave of absence from Kurukshetra University, Kurukshetra, India.

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9. **1**, m.p.=93-5°C, Anal. Calcd for $C_{13}H_{14}O_4IP$: C, 39.82; H, 3.60; I, 32.36; P, 7.90. Found: C, 39.84; H, 3.64; I, 32.19; P, 7.98. **2**, m.p.=121-2°C, Anal. Calcd for $C_{18}H_{16}O_3IP$: C, 49.33; H, 3.68; I, 28.96; P, 7.06. Found: C, 49.06; H, 3.94; I, 28.93; P, 7.00. **3**, m.p.=90-2°C, Anal. Calcd for $C_8H_{12}O_3IP$: C, 30.59; H, 3.85; I, 40.40; P, 9.86. Found: C, 30.53; H, 3.80; I, 40.29; P, 9.78. All products **5a-7e** gave correct results for high resolution mass spectroscopy and/or elemental analysis, except for **5a** and **5d** (off C), **5b**, **5c** and **6d** (off P).
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12. $CDCl_3$ was the solvent for all NMR spectra; chemical shifts are given in ppm and coupling constants in Hz. Chemical shifts are relative to $CDCl_3$ residual protons for ^{1}H NMR and to $CDCl_3$ at 77.0 ppm for ^{13}C NMR. ^{31}P NMR spectra were recorded with decoupler on and were referenced to 85% aq. H_3PO_4 as external standard; chemical shifts downfield of the H_3PO_4 reference are indicated as positive.

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