Direct conversion of secondary phosphine oxides and H-phosphinates with [di(acyloxy)iodo]benzenes to phosphinic and phosphonic amides.

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ABSTRACT:

The reaction of [di(acyloxy)iodo]benzene with secondary phosphine oxides or H-phosphinates in the presence of primary or secondary amines allow one to obtain phosphinic or phosphonic acids amides in the one pot process. We take advantage of the strong acylating system DAIB / $R_2P(O)H$ to phosphinylation of amines. However the reaction mechanism is multi pathway and causes yields of phosphinic or phosphonic acids amides to be moderate. When the concentration of amines are low the intermolecular process plays main role leding to the formation of carboxylic amides through mixed phosphoric-carboxylic anhydride, and also in the low concentration of amines THF effectively compete with the amines in the nucleophilic attack on the acylating intermediates.

INTRODUCTION

Despite the fact that first hypervalent organoiodine compound was synthesized almost two centuries ago by Wilgerodt in 1886 [1], and hypervalent iodine reagents are widely used in organic transformations [2], [3], reactivity of hypervalent organoiodine compound with organophosphorus reagents is still considerably unexplored area. There are only a few publication concerning reactions of usual hypervalent organoiodine regents as [di(acetoxy)iodo]benzene, [bis(trifluoroacetoxy)iodo]benzene, iodozobenzene or dichloroiodobenzene with phosphorus nucleophiles. In 1978 Foss published work concerning oxidation of diphosphines and trialkyl phosphites with iodozobenzene [4]. Lopusinski carried out a set of experiments between phosphoroorganic reagents such as triphenylphosphine, trialkyl phosphites, triarylphosphites with iodozobenzene and iodoxybenzene in the presence of montmorylonite or in the absence such a catalyst [5]. Garreg *et al* tried to use [di(acetoxy)iodo]benzene as a mild reagent for oxidation of H-phosphonates to phosphates in oligonucleotide synthesis [6]. An interesting aspect of the reactivity of hypervalent iodine

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organic compounds with phosphorus nucleophiles is the direct arylation of phosphorus acid salts [7], trialkyl phosphites [8] or phosphines [9] using aryliodonium salts.

Phosphorus analogs of Koser reagent [hydroxy((phosphoryl)oxy)iodo]benzenes and their reactivity exemplify an interesting aspect of hypervalent iodine and phosphororganic chemistry, particularly α-phosphoryloxylation of ketones [10], [11] and preparation of alkynyl dialkyl phophates [12].

In our research we focused on the subject of the reactivity of hypervalent iodine compounds with phosphorus nucleophiles such as dialkyl phosphites, trialkyl phosphites, secondary phosphine oxides, and aryl H-phosphinates as well as on the problem of reactivity of hypervalent iodine compounds with aforementioned phosphorus nucleophiles in the presence of additional nucleophiles, for example, alcohols [13], [14].

As we previously reported, the system [di(acyloxy)iodo]benzene and $R_2P(O)H$ is a strong acylating agent, which is able to acylate various oxygen nucleophiles as alcohols or carboxylic acids [13], [14]. Moreover, the system of the Koser reagent Ph(OTs)OH / $R_2P(O)H$ in the absence of other better nucleophiles is able to acylate even ethers like THF, which demonstrates the acylating power of this system [15].

So far, our research in exploring properties of hypervalent iodine / organophosphorus nucleophile as an acylating system considers only acylation of oxygen species as sufficiently resistant to oxidation by hypervalent iodine compounds to ensure a clean route of reaction. However, now we would like to present results of research in which we examined the acylating properties of the hypervalent iodine / organophosphorus nucleophile system toward acylation of aliphatic amines, an alternative for the Todd-Atherton reaction [16].

RESULTS AND DISCUSSION

As a first we performed an experiment with commercially available [di(acetoxy)iodo]benzene **2** and diphenylphosphine oxide **1** in the presence of isobutyl amine. To take into consideration the higher nucleophilicity of amines compared to the nucleophilicity of alcohols and ethers we performed first experiments with only 3 eq of amine in the THF solution. We had expected that thanks to the high nucleophilicity of amine we would obtain mainly N-isobutyl diphenylphosphinic acid amide **9**.

However after work up and separation of the reaction mixture we did not obtain any traces of N-isobutyl diphenylphosphinic acid amide **9**, instead we isolated diphenylphosphinic acid **5** with 50% yield and O-(diphenylphosphinoyl)-O'-acetyl-1,4-butanediol **8** with 12% yield as a

product of THF ring opening. In further experiments we used [di(benzoyloxy)iodo]benzene as a hypervalent iodine reagent to facilitate isolation of carboxylic amides.

TABLE 1. Reaction of $R^1R^2P(O)H$ with [di(benzoyloxy)iodo]benzene in the presence of amines R^4R^5NH in THF as a solvent.

| Run | R^1, R^2 | R^4 | R^5 | Yields [%] | | |
				5	6	8
1	Ph	H	iBu	66	62	16
2	Bzl	H	iBu	45	21	10
3	Bzl	Et	Et	50	60	20
4	Ph	Et	Et	77	29	14

We performed set of experiments with [di(benzoyloxy)iodo]benzene and diphenylphospine oxide or dibenzylphosphine oxide. The results of these experiments are presented in Table 1. From the reactions mixtures we isolated THF ring opening products **8**, phosphinic acids **5**, and carboxylic amides **6**, we did not isolate of phosphinic acids amides **9**. On the base of these experiments, and taking into consideration our previous works [14], [15], we have proposed tentative mechanism of this reaction presented in the Scheme 1.
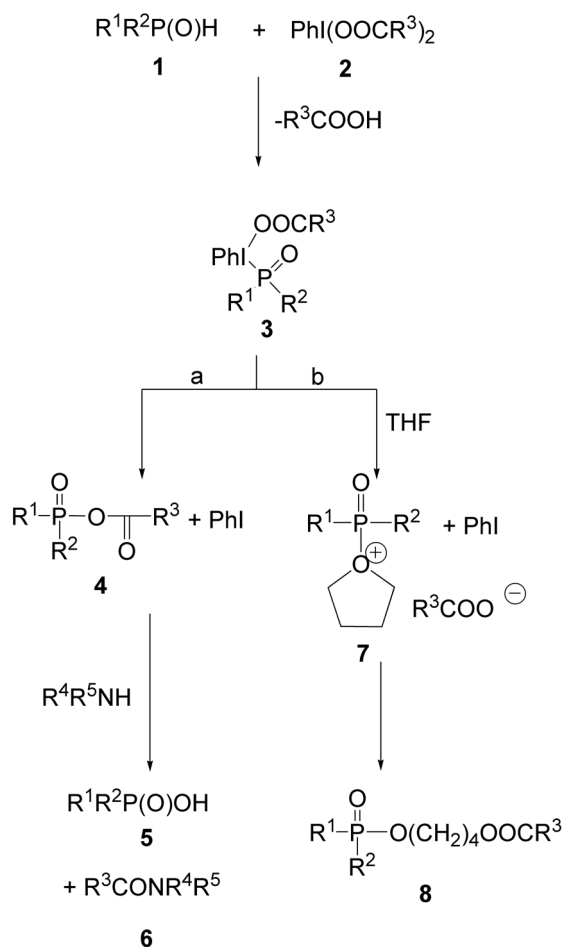
At the first stage the trivalent form of phosphorous nucleophil react with the [di(acyloxy)iodo]benzene and form intermediate **3**, which may undergo reactions in two ways. The first possibility pathway (a) is intermolecular collapse of **3** into phosphoric-carboxylic mixed anhydride, which undergoes further reaction with amine and produces as a final product carboxylic amide. Such a reactions of mixed anhydrides with amines is a well known fast process [17], so we did not isolate mixed anhydride since it was immediately consumed in the reaction with amine. The second possibility of reaction, pathway (b) is reaction of the intermediate **3** with THF which is present in a large excess as a solvent leading to oxonium salt **7**, which undergoes reaction with carboxylic acid anion and produces O-(phosphinoyl)-O'-acyl-1,4-butanediol **8**.

Surprisingly, we did not isolate any product of the nucleophilic attack of amine on the phosphorus atom in the intermediate **3** meaning phosphinic acid amide, which we might expect, taking into consideration much higher nucleophilicity of amines compared to THF, but we had already noticed that the species type of **3** is an extremely reactive acylating agent which we were only able to observe in ^{31}P NMR, but not able to isolate [14]. So if this compound is extremely reactive, its selectivity is poor and probably it reacts quickly in solvent cage with any nucleophile whose concentration is higher. In typical experiment the molar ratio of THF to amine was about (30:1) what explains why we did not isolate phosphinic acid amide.

Because we did not isolate phosphinic acid amides, we run experiments in amines as a solvent to make nucleophilic attack of amine on the **3** possible and to exclude THF opening ring process. We performed experiments in which we treated the solution of $R^1R^2P(O)H$ phosphorus acids in appropriate amine with [di(benzoyloxy)iodo]benzene. From the reaction mixtures we isolated phosphinic acid amides **9**, carboxylic amides **6** and phosphinic acids **5**. The results are presented in the Table 2

TABLE 2. Reaction of $R^1R^2P(O)H$ with [di(benzoyloxy)iodo]benzene in the amines as a solvents.

Run	R^1, R^2	R^4	R^5	Yields [%]		
				5	**6**	**9**
5	Ph	Et	Et	34	29	34
6	Ph	H	iBu	38	60	34
7	n-Hex	Et	Et	43	18	11

Because of higher concentration of amines we were able to push the reaction via pathway (c) Scheme 2 to produce phosphinic acid amide. However, intermolecular pathway (b) Scheme 1 which led to mixed phosphoric-carboxylic anhydride and in the further reaction with amine to carboxylic amide, was still present. It must be point that formation of **9** may result not only by the pathway (c), beside the nucleophilic attack on the phosphorus atom in the intermediate **3** we have to consider alternative pathway (d) with ligand exchange acyloxy group with amine with the formation of intermediate **3a** and subsequent intermolecular reaction leading to amide **9** and PhI. However at this moment we don't have rational arguments to exclude or confirm one of them.
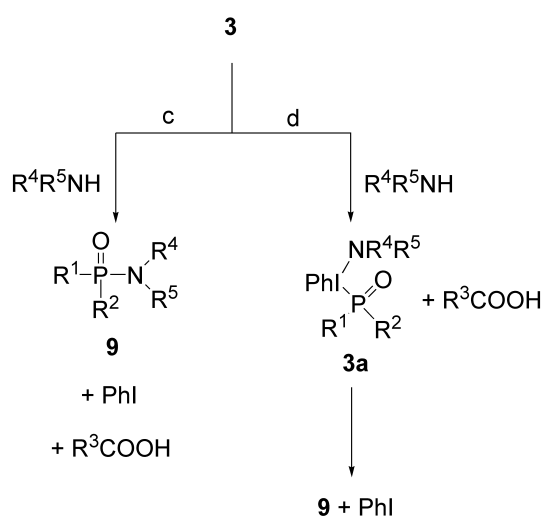
To confirm proposed mechanism and to exclude possibility that carboxylic amide is formed in the reaction [di(acyloxy)iodo]benzene) with amine we run an independent experiment with [di(benzoyloxy)iodo]benzene) in the excess of iso-butylamine as a solvent without **1** in which we did not observe the formation of any traces of **6**. Despite the cited reactions mixed phosphorus-carboxylic anhydrides with amines [17], in order to additionally confirm that in the case of our model of anhydride only **6** is produced in the reaction of mixed phosphinic-carboxylic anhydride with amine, we performed an experiment using diphenylphosphinic-benzoic anhydride obtained on the independent way (from diphenylphosphinic acid salt and acetyl chloride) with N,N-diethylamine, and in this reaction we observed only formation of carboxylic amide without any traces of phosphinic amide.

Taking into consideration that in performed experiments phosphorus amides were produced in one top process directly from secondary phosphine oxides or H-phosphinates similarly as in the Todd-Atherton reaction, we run a set of experiments between commercially available [di(acetoxy)iodo]benzene and $R^1R^2P(O)H$ acids in the excess of amines to check the possibility of using the explored reaction for the quick preparation of phosphinic or

phosphonic acids amides. The results are presented in Table 3. From the reactions mixtures we have isolated phosphoric acids amides and also phosphinic or phosphonic acids, which confirms the competition of both processes by the pathway (a) and (c) and causes yields of phosphinic or phosphonic acids amides to be moderate.

Table 3. Reaction of $R^1R^2P(O)H$ with [di(acetoxy)iodo]benzene in the amines as solvents.

Run	R^1	R^2	R^4	R^5	Yields [%]	
					5	**9**
8	Ph	Ph	H	n-Bu	33	34
9	Bzl	Bzl	H	n-Bu	54	30
10	Ph	iPrO	H	n-Bu	55	16
11	Ph	Ph	$(CH_2)_2O(CH_2)_2$	53	19	
12	n-Hex	n-Hex	$(CH_2)_2O(CH_2)_2$	20	22	
13	Ph	iPrO	H	iBu	46	17

EXPERIMENTAL

All reactions were carried out under argon atmosphere in dry solvents (THF was dried over potassium, chloroform over P_2O_5, amines over KOH). Chromatography was carried out on Silica Gel 60 (0.15-0.3 mm) Macherey Nagel[®]. ^{31}P NMR and ^1H NMR spectra were recorded with a Varian apparatus at 200 or 500 MHz. [Di(acetoxy)iodo]benzene was purchased from Avocado.

[Di(benzoyloxy)iodo]benzene

[Di(benzoyloxy)iodo]benzene was obtained by the modification method described in literature [18]. 10 mmol [di(acetoxy)iodo]benzene and 20 mmol of benzoic acid was disolved in 40 ml of $CHCl_3$ folowed by five times reapeated slow evaporation under reduced presure portions of 40 ml $CHCl_3$. Residue finally was crystallized from $CHCl_3$ / Hexane. Yield 3.12 g 70% mp = 155-157°C

General procedure for the reactions of $R^1R^2P(O)H$ with [di(benzoyloxy)iodo]benzene in the presence of amines in THF as a solvent. [Runs 1-4]

To a solution of **1** (2 mmol) in THF (20 ml) amine (8mmol) and [di(benzoyloxy)iodo]benzene (2 mmol, 0,892g) was added. Reaction mixture was stirred under Argon at R.T for 15 h. Solvent was removed under reduced pressure, and the residue was dissolved in Et$_2$O (50ml), Et$_2$O was washed with 5% NaHCO$_3$ (3x5ml) and 2M HCl (2x5ml), dried with MgSO$_4$, solvent was removed under reduced pressure and residue was purified by column chromatography over silica gel (chloroform-acetone, 15:1) to obtain: **6** and **8**. Alkaline water layer was acidified with conc. HCl and extracted with AcOEt (3x30ml) dried with MgSO$_4$, solvent was removed under reduced pressure and residue was crystallized from (AcOEt-Hexane) to obtain **5.**

Run 1*:* O-(diphenylphosphinoyl)-O'-benzoyl-1,4-butanediol (126 mg, 16%).^{1}H NMR (200MHz, CDCl$_3$) δ 1.9 (m, 4H), 4.05÷4.15 (m, 2H), 4.3÷4.4 (m, 2H), 7.35÷7.6 (m, 9H), 7.75÷7.9 (m, 4H), 8÷8.08 (m, 2H); ^{31}P NMR (300MHz, CDCl$_3$) δ 34.38; N-isobutyl benzamide (220 mg, 62%);   Diphenylphosphinic acid (292 mg, 66%) mp= 189-191°C. ^{31}P NMR (300MHz, CDCl$_3$) δ 34.18

Run 2: O-(dibenzylphosphinoyl)-O'-benzoyl-1,4-butanediol (80 mg, 10%).^{1}H NMR (200MHz, CDCl$_3$) δ 1.53÷1.78 (m, 4H), 3.05 (t, J^{PH}=15 Hz, 4H), 3.85 (t, 2H), 4.25 (t, 2H), 7.1÷7.7 (m, 15H); ^{31}P NMR (300MHz, CDCl$_3$) δ= 51.26; N-isobutyl benzamide (70 mg, 21%); Dibenzylphosphinic acid (220 mg, 45%) mp= 187-189°C, ^{31}P NMR (300MHz, CDCl$_3$) δ 52.36

Run 3*:* O-(dibenzylphosphinoyl)-O'-benzoyl-1,4-butanediol (160 mg, 20%).^{1}H NMR (200MHz, CDCl$_3$); N,N-diethyl benzamide (212 mg, 60%); Dibenzylphosphinic acid (246 mg, 50%)

Run 4: O-(diphenylphosphinoyl)-O'-benzoyl-1,4-butanediol (110 mg, 14%).; N,N-diethyl benzamide (102 mg, 29%);   Diphenylphosphinic acid (335 mg, 77%).

General procedure for the reactions of R^{1}R^{2}P(O)H with [di(benzoyloxy)iodo]benzene in the amines as a solvents. [Runs 5-7]

To a solution of **1** (2 mmol) in amine (100 mmol) [di(benzoyloxy)iodo]benzene (2 mmol, 0,892g) was added. Reaction mixture was stirred under Argon at R.T for 15 h.

Solvents was removed under reduced pressure, and the residue was dissolved in Et$_2$O (50ml), Et$_2$O was washed with 5% NaHCO$_3$ (3x5ml) and 2M HCl (2x5ml), dried with MgSO$_4$, solvent was removed under reduced pressure and residue was purified by column chromatography over silica gel (chloroform-acetone, 15:1) to obtain: **6** and **9**. Alkaline water layer was acidified with conc. HCl and extracted with AcOEt (3x30ml) dried with MgSO$_4$, solvent was removed under reduced pressure and residue was crystallized from (AcOEt-Hexane) to obtain **5.**

Run 5: N,N-diethyl diphenylphosphinic acid amide (185 mg, 34%) ^{1}H NMR (200MHz, CDCl$_3$) δ 1.09 (t, 6H), 3.11 (m, 4H), 7.34÷7.56 (m, 6H), 7.78÷7.94 (m, 4H); N,N-diethyl benzamide (113 mg, 32%); Diphenylphosphinic acid (148 mg, 34%).

Run 6: N-isobutyl diphenylphosphinic acid amide (185 mg, 34%) ^{1}H NMR (200MHz, CDCl$_3$) δ 0.9 (d, 6H), 1.8 (m, 1H), 2.8 (t, J=7.14 Hz, 2H), 3.1÷3.45 (bs, 1H), 7.32÷7.73 (m, 6H), 7.95÷8.14 (m, 4H), ^{31}P NMR (300MHz, CDCl$_3$) δ 27.45; N-isobutyl benzamide (212 mg, 60%); Diphenylphosphinic acid (165 mg, 38%).

Run 7: N,N-diethyl di-n-hexylphosphinic acid amide (64 mg, 11%).^{1}H NMR (200MHz, CDCl$_3$) δ 0.8÷1.75 (m, 32H), 2.9÷3.17 (m, 4H); ^{31}P NMR (300MHz, CDCl$_3$) δ= 50.72; N,N-diethyl benzamide (64 mg, 18%); di-n-hexylphosphinic acid (201 mg, 43%), ^{31}P NMR (300MHz, CDCl$_3$) δ 52.36.

General procedure for the reactions of R^{1}R^{2}P(O)H with [di(acetoxy)iodo]benzene in the amines as solvents. [Runs 8-13]

To a solution of **1** (2 mmol) in amine (100 mmol) [di(acetoxy)iodo]benzene (2 mmol, 0.64g). was added Reaction mixture was stirred under Argon at R.T for 15 h. Solvents was removed under reduced pressure, and the residue was dissolved in Et$_2$O (50ml), Et$_2$O was washed with 5% NaHCO$_3$ (3x5ml) and 2M HCl (2x5ml), dried with MgSO$_4$, solvent was removed under reduced pressure and residue was purified by column chromatography over silica gel (chloroform-acetone, 15:1) to obtain: **9**. Alkaline water layer was acidified with conc. HCl and extracted with AcOEt (3x30ml) dried with MgSO$_4$, solvent was removed under reduced pressure and residue was crystallized from (AcOEt-Hexane) to obtain **5.**

Run 8: N-n-butyl diphenylphosphinic acid amide (185 mg, 34 %) ^{1}H NMR (200MHz, CDCl$_3$) δ 0.85 (t, 3H), 1.32 (m, 2H), 1.53 (m, 2H), 2.93 (m, 3H), 7.41 (m, 6H), 7.88 (m, 4H), ^{31}P NMR (300MHz, CDCl$_3$) δ 24.72; Diphenylphosphinic acid (143 mg, 33%).

Run 9: N-n-butyl dibenzylphosphinic acid amide (180 mg, 30%).^{1}H NMR (500MHz, CDCl$_3$) δ 0.85 (t, 3H), 1.23 (m, 2H), 1.36 (m, 2H), 2.85 (q, 2H), 3.09 (m, 4H), 7.26 (m, 6H), 7.33 (m,4H), ^{31}P NMR (300MHz, CDCl$_3$) δ= 38.42; Dibenzylphosphinic acid (265 mg, 45%).

Run 10: N-n-butyl O-isopropyl phenylphosphonic acid amide (82 mg, 16%) ^{1}H NMR (500MHz, CDCl$_3$) δ 0.85 (t, 3H), 1.26 (m, 2H), 1.29 (d, 3H), 1.36 (d, 3H), 1.42 (m, 2H), 2.84 (m, 3H), 4.74 (m, 1H), 7.44 (m,3H), 7.80 (m, 2H), ^{31}P NMR (300MHz, CDCl$_3$) δ= 22.56; Isopropyl phenylphosphonate (224 mg, 56%)

Run11: 4-diphenylphosphinoyl-morpholine (109 mg, 19 %) ^{1}H NMR (500MHz, CDCl$_3$) δ 3.07 (m, 4H), 3.70 (m, 4H), 7.47 (m, 6H), 7.87 (m, 4H), ^{31}P NMR (300MHz, CDCl$_3$) δ 30.25; Diphenylphosphinic acid (239 mg, 55%)

Run 12: 4-(di-n-hexylphosphinoyl)-morpholine (133 mg, 22 %), ^{1}H NMR (500MHz, CDCl$_3$) δ 0.87 (t, 6H), 1.25-1.31 (m, 12H), 1.58-1.66 (m, 8H), 3.04 (m, 4H), 3.66 (m, 4H), ^{31}P NMR (300MHz, CDCl$_3$) δ 49.28; Di-n-hexylphosphic acid (34 mg, 20%)

Run13: N-isobutyl O-isopropyl phenylphosphonic acid amide (85 mg, 17%), ^{1}H NMR (200MHz, CDCl$_3$) δ 0.85 (dd, 6H), 1.35 (dd, 6H), 1.62 (m, 1H), 1.36 (d, 3H), 2.65 (t, 2H), 2.96 (bs, 1H), 4.72 (m, 1H), 7.44 (m,3H), 7.80 (m, 2H); Isopropyl phenylphosphonate (184 mg, 46%)

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