The system $PhIO/Ph_3P$ as an efficient reagent for mild and direct coupling of alcohols with carboxylic acids

Maria A. Boulogeorgou, Virginia V. Triantakonstanti and John K. Gallos*

Department of Chemistry, Aristotle University of Thessaloniki, Thessaloniki 541 24, Greece
E-mail: igallos@chem.auth.gr

Dedicated to Prof. Michael Orfanopoulos on the occasion of his official retirement, to acknowledge his contribution to physical and synthetic organic chemistry

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Abstract

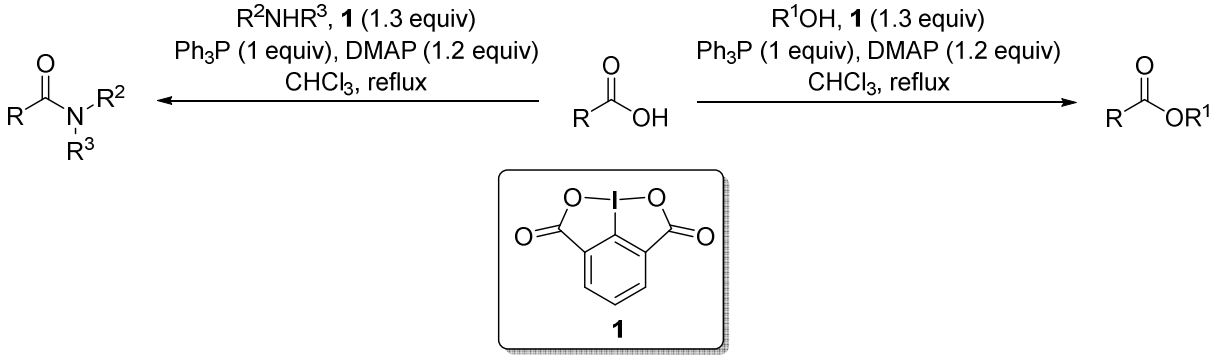
The $PhIO/Ph_3P$ system acts as an efficient mild reagent for the direct esterification of carboxylic acids with alcohols. (Diacyloxyiodo)benzenes, which are *in situ* generated in DCM solution from carboxylic acids and iodosylbenzene, react smoothly with triphenylphosphine and an alcohol at refluxing DCM in the presence of catalytic amount of DMAP to give the respective esters from good to high yields.

Keywords: (Diacyloxyiodo)benzenes, iodosylbenzene, carboxylic acids, alcohols, carboxylic esters, triphenylphosphine

Introduction

Ester functionality is widely present among a variety of natural products, lipids, pharmaceuticals, polymers, perfumes, food preservatives, cosmetics and synthetic materials of current interest.[1] Accordingly, its importance continues to feed interest in research towards the discovery of new formation methods. Further to the numerous classical synthetic methods which have been developed so far, the direct coupling of alcohols with carboxylic acids are of particular importance.[2] This transformation often requires special equipment or dehydrating agents and always the presence of coupling reagents, which are usually metal salts and organometallic reagents. These reagents and dehydrating agents are often toxic and/or expensive. As such, remains a need to develop mild and efficient methods towards the effective formation of ester functionality, using environmentally benign and readily recyclable coupling reagents. Such requirements are often met in the hypervalent iodine reagents,[3] whose chemistry has experienced remarkable growth during the last decades mainly in oxidation processes.[4-17]

In the light of these properties of organoiodine reagents, Zhang *et al.*,[18] reported recently a method of broad scope for the coupling of carboxylic acids with amines or alcohols, using the hypervalent iodine lactone **1** as coupling reagent (Scheme 1). Treatment of carboxylic acids with amines or alcohols in the presence of lactone **1**, triphenylphosphine and dimethylaminopyridine (DMAP), gave respective amides or esters in high yields. However, the use of all reagents, including lactone **1**, which was costly to prepare, in stoichiometric amount as well the necessity for prolonged heating in chloroform at reflux are drawbacks for the method. Attempts to replace **1** with (diacetoxyiodo)benzene (PIDA) or [bis(trifluoroacetoxy)iodo]benzene (PIFA) led to the respective acetates as main products.



Scheme 1. Coupling of carboxylic acids with amines and alcohols a hypervalent iodine reagent.

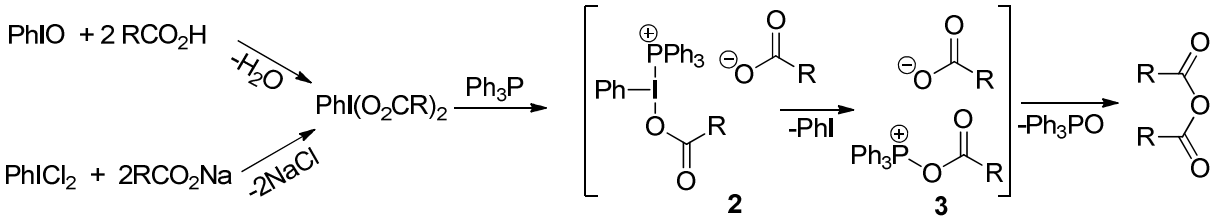
Our experience in hypervalent iodine chemistry[19-29] prompted us to investigate the possibility to simplify Zhang's protocol by using more readily available reagents and milder conditions to overcome their disadvantages. Herein, we report our first promising results.

Results and Discussion

Many years ago, Varvoglis and one of us reported that the reaction of (diacyloxyiodo)benzenes with triphenylphosphine afforded the respective carboxylic acid anhydrides, which were isolated chromatographically (Scheme 2).[30] The dicarboxylates were prepared *in situ* by reaction of iodosylbenzene (PhIO) with carboxylic acids or from dichloroiodosobenzene with sodium carboxylates. The formation of intermediates **2** and **3** was postulated and evidence for the *in situ* generation of **3** was provided.

Taking into account the above findings, we considered that a reaction of (diacyloxyiodo)-benzenes with triphenylphosphine in the presence of an alcohol could afford the respective ester *via* a nucleophilic attack to intermediate **3** by the alcohol. Since the (diacyloxyiodo)benzenes can be prepared *in situ* from iodosylbenzene (PhIO) and carboxylic acids this approach would lead to

the esterification of added alcohols. Worthy to note was that a similar intermediate to **3** was also proposed by Zhang *et al.*[18]

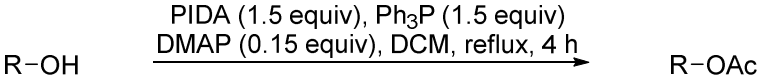


Scheme 2. Conversion of carboxylic acids into anhydrides *via* (diacyloxyiodo)benzenes.

To this end, we initially studied the reaction of a number of alcohols with the commercially available (diacetoxyiodo)benzene (PIDA) in the presence of triphenylphosphine and an organic base, expecting the formation of the respective acetates. The best results were obtained when the reaction was carried out in dichloromethane (DCM) heated at reflux using 1.5 equivalents of each of PIDA and Ph_3P and 0.15 equivalents of DMAP as a base (Table 1). Longer reaction times were required and lower yields were obtained at room temperature or when Et_3N or pyridine were used as base.

An inspection of Table 1 reveals that primary and secondary alcohols were readily acetylated in mild conditions and high yields. In contrast, acetylation of tertiary alcohols was unsuccessful, and the alcohols were recovered. Interestingly, trifluoroacetylation was easily achieved (entry 2). These findings indicate that the system PIDA/Ph_3P can be used as a mild reagent for protection of primary and secondary alcohols.

Table 1. Acetylation of alcohols with PIDA



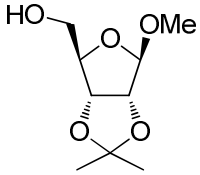
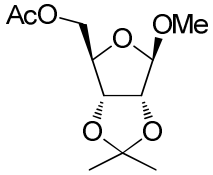
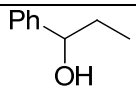
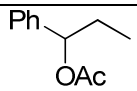
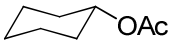
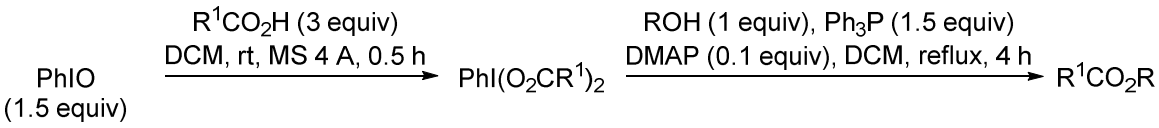
Entry	ROH	ROAc	Yield (%)[b]	Ref.
1	$PhCH_2CH_2OH$	$PhCH_2CH_2OAc$	93	31
2[a]	$PhCH_2CH_2OH$	$PhCH_2CH_2O_2CCF_3$	92	32
3	$PhCH_2OH$	$PhCH_2OAc$	77	31
4	$CH_3(CH_2)_6CH_2OH$	$CH_3(CH_2)_6CH_2OAc$	81	33
5			98	-

Table 1 (continued)

Entry	ROH	ROAc	Yield (%)[b]	Ref.
6			89	34
7			82	31
8	Me_3COH	Me_3COAc	0	
9	Ph_3COH	Ph_3COAc	0	

[a] PIFA was used instead of PIDA; [b] Yields were based on alcohol.

Table 2. Coupling of carboxylic acids with alcohols using PhIO as a coupling reagent



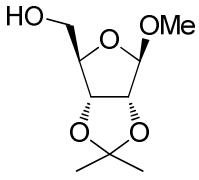
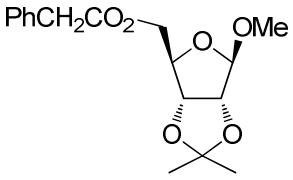
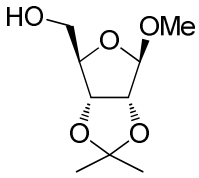
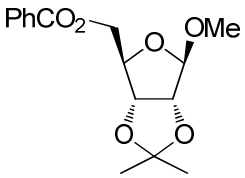
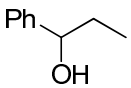
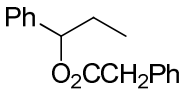
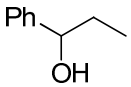
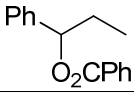
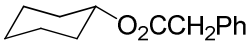
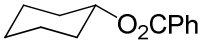
Entry	ROH	R^1CO_2H	R^1CO_2R	Yield (%)[a]	Ref.
1	$PhCH_2CH_2OH$	$PhCH_2CO_2H$	$PhCH_2CO_2CH_2CH_2Ph$	85	35
2	$PhCH_2CH_2OH$	$PhCO_2H$	$PhCO_2CH_2CH_2Ph$	77	31
3	$CH_3(CH_2)_6CH_2OH$	$PhCH_2CO_2H$	$PhCH_2CO_2CH_2(CH_2)_6CH_3$	67	36
4	$CH_3(CH_2)_6CH_2OH$	$PhCO_2H$	$PhCO_2CH_2(CH_2)_6CH_3$	66	37
5		$PhCH_2CO_2H$		58	-
6		$PhCO_2H$		59	38
7		$PhCH_2CO_2H$		73	39
8		$PhCO_2H$		78	34

Table 2 (continued)

Entry	ROH	R^1CO_2H	R^1CO_2R	Yield (%)[a]	Ref.
9		$PhCH_2CO_2H$		63	40
10		$PhCO_2H$		64	41

[a] Yields were based on alcohol.

Taking into account these results, we turned our attention to widening the scope of the method by using carboxylic acids as starting materials and converting them *in situ* to the respective (diacyloxyiodo)benzenes in DCM solution, before the addition of triphenylphosphine and an alcohol. In a typical procedure, the carboxylic acid and PhIO were treated in DCM at rt under stirring in the presence of molecular sieves, until the dissolution of the latter (< 30 min). Then the alcohol, DMAP and triphenylphosphine were added, and after 4 h heating at reflux, the solvent was evaporated and the mixture chromatographed on a silica gel column. The results are depicted in Table 2.

In general, yields, which were not optimized, are somewhat lower than those in Table 1, but it is reasonably expected from a two-step one-pot reaction compared to a one-step reaction. All esters prepared are known compounds (with the exception of two *D*-ribose derivatives) and unequivocally characterized from their NMR data, which were identical to those reported in the literature.[31-41]

Compared to the Zhang protocol, our method applies milder condition, lower temperatures, shorter reaction times and avoids the toxic chloroform as solvent. The base (DMAP) is used catalytically (10-15%), and the organoiodine coupling reagent is cheap and readily available. In addition, the system PIDA/Ph_3P can be applied for protection of primary and secondary alcohols. Further work to establish the scope and limitations of the PhIO/Ph_3P system is underway.

Experimental Section

General procedure for acetylation of alcohols with PIDA and Ph_3P (Table 1). Alcohol (1 mmol), DMAP (18 mg, 0.15 mmol) and Ph_3P (393 mg, 1.5 mmol) in this order were successively added to a solution of PIDA (483 mg, 1.5 mmol) in dry DCM (15 mL) and the resulting mixture was heated at reflux for 4 h, under an argon atmosphere. The solvent was then evaporated off and the residue was chromatographed on a silica gel column (*c*-hexane/EtOAc) to give firstly the PhI formed and any unreacted Ph_3P, followed by the desired ester in yields given in Table 1.

Methyl 5-*O*-Acetyl-2,3-*O*-isopropylidene-β-*D*-ribofuranoside (Table 1, entry 5) (241 mg, 98%) was isolated as a colorless oil. $[\alpha]_D$ -82.3 (*c* 3 $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ_H 1.33 (s, 3H), 1.49 (s, 3H), 2.09 (s, 3H), 3.32 (s, 3H), 4.06-4.15 (m, 2H), 4.36 (t, 1H, *J* 7.1 Hz) 4.60 (d, 1H, *J* 5.9 Hz) 4.66 (d, 1H, *J* 5.9 Hz) 4.98 (s, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 20.8, 25.0, 26.4, 54.9, 64.6, 81.9, 84.2, 85.2, 109.4, 170.6 ppm. HRMS *m/z* 247.1178. Calc. for $[C_{11}H_{18}O_6 + H^+]$: 247.1182.

General procedure for eterification of alcohols with carboxylic acids by PhIO and Ph_3P (Table 2). A mixture of carboxylic acid (3 mmol) and PhIO (330 mg, 1.5 mmol) in dry DCM (15 mL) was stirred at ambient temperature in the presence of molecular sieves 4 Å, until complete dissolution (~30 min). The alcohol (1 mmol), DMAP (12 mg, 0.1 mmol) and Ph_3P (393 mg, 1.5 mmol) in this order were then successively added to the clear solution and the resulting mixture was heated at reflux for 4 h, under an argon atmosphere. The solvent was then evaporated off and the residue was chromatographed on a silica gel column (*c*-hexane/EtOAc) to give firstly the PhI formed and any unreacted Ph_3P, followed by the desired ester in yields given in Table 2.

Methyl 5-*O*-phenylacetyl-2,3-*O*-isoplopylidene-β-*D*-ribofuranoside (Table 2, entry 5) (316 mg, 98%) was isolated as a colorless oil. $[\alpha]_D$ -41.9 (*c* 2.8 $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ_H 1.31 (s, 3H), 1.48 (s, 3H), 3.26 (s, 3H), 3.66 (s, 2H), 4.08-4.18 (m, 2H), 4.38 (t, 1H, *J* 6.9 Hz) 4.56 (d, 1H, *J* 6.0 Hz) 4.62 (d, 1H, *J* 6.0 Hz) 4.96 (s, 1H), 7.25-7.35 (m, 5H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 24.9, 26.4, 41.2, 54.9, 65.0, 81.8, 84.1, 85.2, 109.4, 127.1, 128.6, 129.3, 133.7, 171.1 ppm. HRMS *m/z* 323.1497. Calc. for $[C_{17}H_{23}O_6 + H^+]$: 323.1495.

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