Phenyliodine(III) bis(trifluoroacetate) (PIFA)

Georg Pohnert*

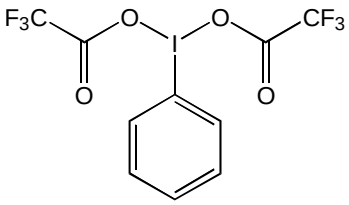
Jena, Max-Planck-Institut für Chemische Ökologie

Received June 30th, 2000

Keywords: Hypervalent compounds, Iodine, Oxidations, Reagents, Pummerer reaction

Contents

Hypervalent iodine reagents are extensively used in synthetic organic chemistry [1]. Known since Willgerodt's first preparation of Ph–ICl_2 in 1886, these reagents have become more than just powerful oxidizing agents. Commercially available reagents like phenyliodine(III) bis(trifluoracetate) (PIFA) **1** (also named [bis-(trifluoroacetoxy)-iodo]-benzene) have received considerable attention.

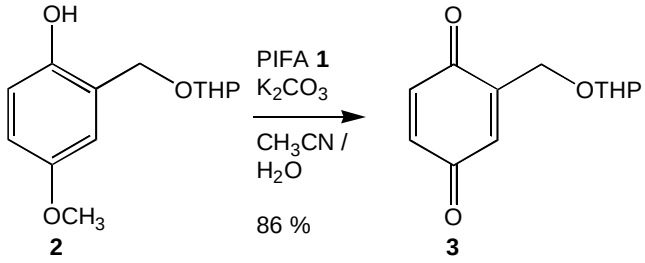


PIFA **1**

This success can be attributed to the chemical properties and reactivities of **1**, which are similar to those of heavy metal reagents, but with low toxicity. Related reagents like phenyliodine(III) diacetate with decreased – or pentafluorophenyliodine(III) bis(trifluoroacetate) with increased – oxidative capabilities are also available, providing a useful selectivity for organic synthesis. The by-product of transformations with **1** is iodobenzene, which can be recycled and is environmentally safe. From a practical point of view, most reactions with PIFA **1** are remarkably simple. They are usually carried out at room temperature in common solvents without special precautions for the exclusion of oxygen or water.

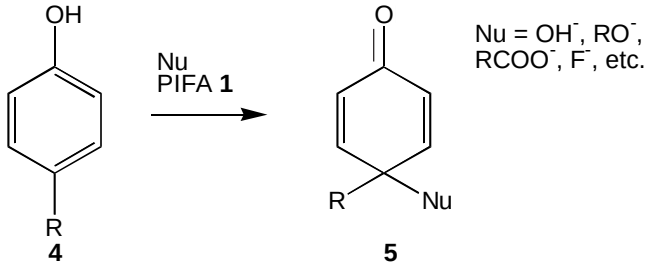
1. Oxidative Transformations of Phenols and Derivatives Using PIFA 1

The oxidative properties of PIFA **1** are similar to those of Tl(III), Hg(II) and Pb(IV) derivatives. One useful application of the reagent lies in the oxidative transformation of phenols. PIFA **1**, for example, is a suitable reagent for the transformation of *p*-alkoxy phenols or 1,4-dihydroxybenzene derivatives to 1,4-benzoquinones [2]. The oxidation is carried out under mild conditions and even acid sensitive substrates can be transformed in good yields in acetonitrile/water when potassium carbonate is added to the reaction mixture (Scheme 1).



Scheme 1 PIFA **1** allows the oxidation of even acid labile substrates like **2** to 1,4-benzoquinones

Transformation of 4-substituted phenols with PIFA **1** in the presence of nucleophiles gives 4,4-disubstituted cyclohexadienones (Scheme 2) [3]. Nucleophiles such as alcohols, amides, fluoride ions, and carboxylic acids have been used widely in inter- or intramolecular reactions.



Scheme 2 Reaction of *para*-substituted phenols in the presence of nucleophiles

Particularly useful is the oxidative transformation of phenols in which carbon–carbon bond formation is achieved. One example is the PIFA **1** mediated formation of the sponge al-

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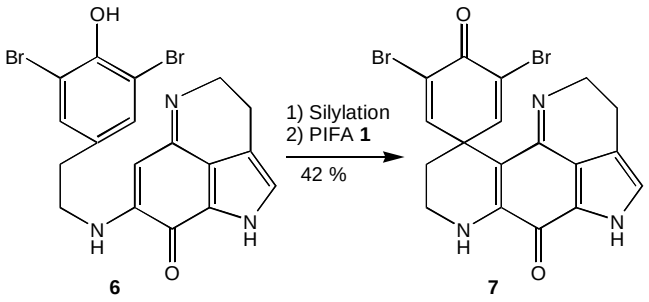
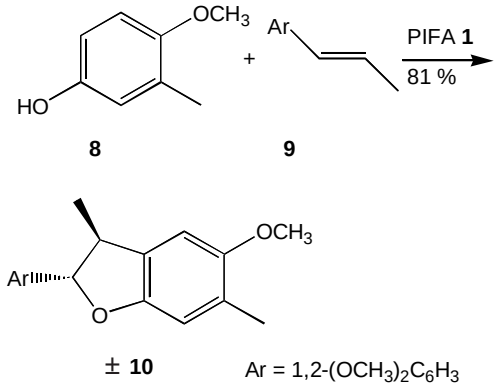
kaloid discorhabdin C **7** (Scheme 3) [4]. The aza spiro dienone formation from *O*-silylated phenol derivatives was also applied to a variety of different heterocylic substrates.



Scheme 3 PIFA **1** mediated cyclization in the synthesis of discorhabdin C **7**

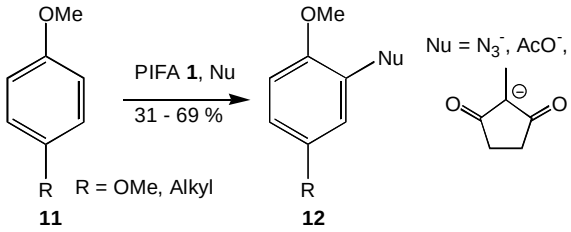
PIFA **1** mediated transformation of *p*-methoxyphenols, like **8**, with electron rich styrene derivatives affords dihydrobenzofurans in a formal 1,3-oxidative cycloaddition. In a comparative study, the authors could show that PIFA **1** represents a chemical equivalent of the electrochemical reaction, with surprisingly similar products and yields [5].



Scheme 4 Preparation of dihydrobenzofuranes

2. Nucleophilic Substitution of Phenol Ethers

In the presence of PIFA **1**, *para*-substituted phenol ethers do not undergo the nucleophilic addition reactions described above. Kita's group showed, in UV-vis and ESR studies, that substrates of type **11** react in a nucleophilic substitution *via* cation radicals as reactive intermediates. These are formed through electron transfer with PIFA **1** and undergo addition reactions in the presence of a variety of nucleophils like trimethylsilylazide or β-dicarbonyl compounds [6]. The substitution products were obtained after stirring phenol ethers for 15 min at room temperature in hexafluoro-2-propanol with PIFA **1** (Scheme 5).

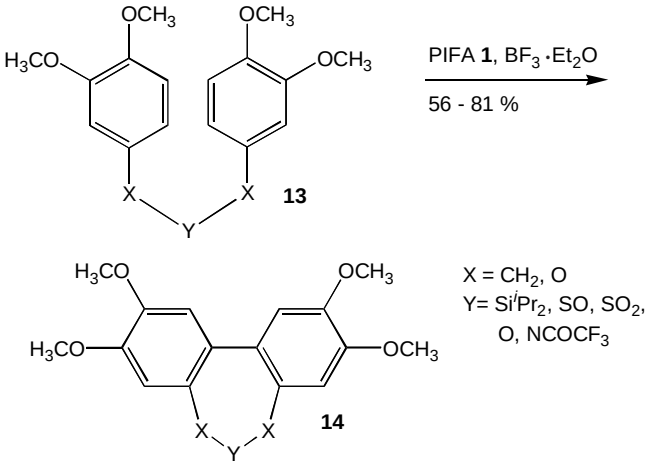


Scheme 5 Use of PIFA **1** in nucleophilic substitution reactions

3. Oxidative Biaryl Coupling

The same type of cationic radical intermediate is involved in the transformation of highly substituted precursors, like **13**, to biaryls [7]. PIFA **1**/$BF_3{\cdot}Et_2O$ reacts with a broad range of substrates to give the biaryl products in good to excellent yields (Scheme 6) [7].

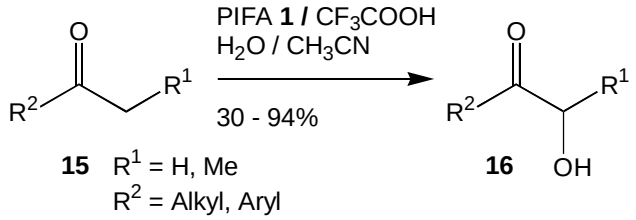
Here, the Lewis acid co-ordinates to the trifluoroacetoxy ligands of PIFA **1** and activates the reagent, thereby allowing the biaryl coupling reactions to be carried out at – 40 °C. Even highly functionalized unsymmetrical products were formed in satisfactory yields and the method proved to be superior to alternative reactions involving heavy metal oxidants.



Scheme 6 Lewis acid activated PIFA **1** in biaryl coupling reactions

4. α-Hydroxylation of Enolizable Ketones

The oxidative power of PIFA **1** can also be used in the functionalization of enolizable ketones, and the direct α-hydroxylation under acidic conditions is a particularly useful reaction (Scheme 7) [8]. The method works well for α-methylketones (**15** R^1 = H) while α-methylenketones (**15** R^1 = CH_3) give lower yields, presumably due to the steric interactions between the bulky hypervalent iodine reagent and the substrates.

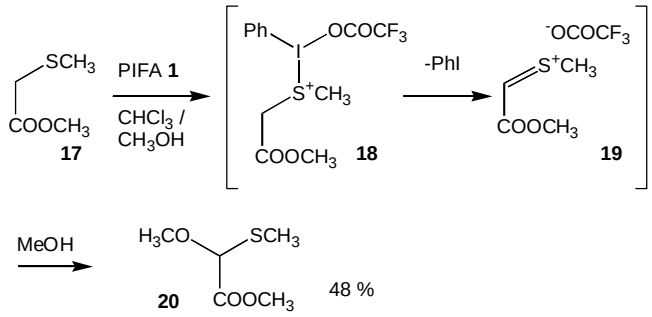


Scheme 7 A mild α-hydroxylation method

A proposed mechanism for this hydroxylation involves initial electrophilic addition of PIFA **1** to the enolized ketone and subsequent nucleophilic substitution of the iodonium intermediate. In the presence of appropriate external nucleophiles this reaction may afford the respective α-substituted ketones [9].

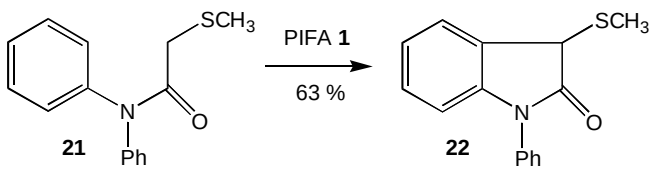
5. Pummerer Type Reactions

Treatment of α-acylsulfides like **17** with PIFA **1** results in a Pummerer-type reaction [10]. The transformation is thought to proceed through the intermediate **18**, which is formed by attack of PIFA **1** on the sulphur atom followed by elimination of an acidic α-proton and iodobenzene to give the Pummerer reaction intermediate **19**. In the presence of MeOH the cation reacts to produce the α-methoxy-α-(methylthio) acetate **20** in 48% yield (Scheme 8).



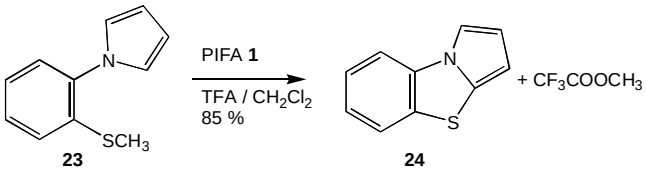
Scheme 8 Mechanism of the PIFA **1** mediated Pummerer reaction

Intramolecular Friedel-Crafts type carbon–carbon bond formation was achieved when **21** was stirred with 1.2 equivalents PIFA **1** at room temperature in 1,2-dichloroethylene (Scheme 9) [10].



Scheme 9 Intramolecular Friedel-Crafts type cyclization

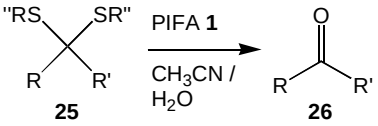
If the substrates lack an activating group on the carbon alpha to the sulfide, the intermediate thionium ions of type **19** can not be generated by hydrogen abstraction and products of an interrupted Pummerer reaction result. This sequence was applied to the formation of pyrrolo[2,1-*b*]-benzothiazole **24** from the simple sulfide **23** (Scheme 10) [11].



Scheme 10 Interrupted Pummerer reaction

6. Deprotection of Thioacetals with PIFA 1

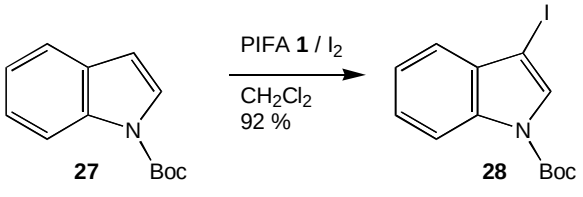
The fast and efficient method for dethioacetalization using PIFA **1** has found numerous applications. Under mild conditions a wide range of thioacetals and thioketals can be deprotected to the corresponding carbonyls with excellent yields in acetonitrile/water (Scheme 11) [12]. The reaction conditions are compatible with a variety of other functional groups, such as -COSPh, HO-, TsO- and R_2N-. PIFA **1** is therefore the reagent of choice for deprotection of complex intermediates in natural product synthesis.



Scheme 11 A mild and convenient deprotection of thioacetals

7. Iodination Using Iodine in the Presence of PIFA 1

PIFA **1** treated with iodine in CCl_4 or pyridine/CH_2Cl_2 gives mild iodinating reaction mixtures (Scheme 12). These solutions can be used for the selective iodination of unsaturated ketones [13] or heterocyclic compounds like *N*-Boc-protected indole **27**, uracil, *n*-alkylpyridin-2-one [13], and substitut-

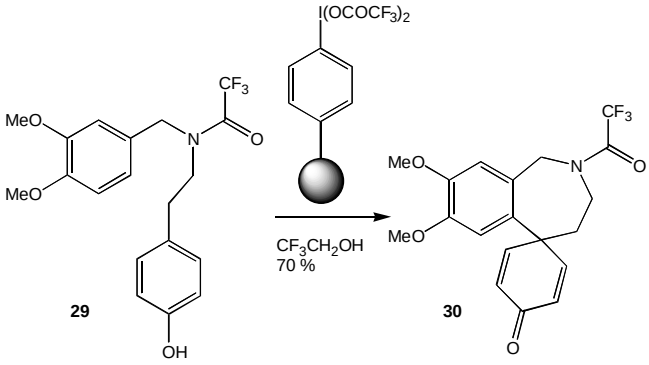


Scheme 12 Iodination in the presence of PIFA **1** and iodine

ed thiophenes [14]. The selectivity of the reactions was remarkable and no products from multiple iodination could be detected in the examples presented.

8. Polymer Supported PIFA 1

Polymer supported PIFA **1** was introduced recently as a further development of the reagent. The resin bound hypervalent iodine was used in an elegant five-step synthesis of the alkaloid oxomarithidine that was entirely based on the use of different polymer supported reagents. The phenolic cyclization to **30** proceeded smoothly in the presence of resin bound PIFA **1** (70% yield) and work-up only involved filtration, followed by evaporation of the solvent (Scheme 13) [15].



Scheme 13 Use of polymer supported PIFA **1** in the synthesis of oxomarithidine

In conclusion, PIFA **1** and other related hypervalent iodine(III) reagents have turned out to be mild and convenient tools in organic synthesis. Their use in numerous natural product syntheses and the continuous development of new synthetic methods shows promising perspectives. Reactions involving PIFA **1** can at least partially replace highly toxic heavy metal salts with similar reactive properties.

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Address for correspondence:
Dr. Georg Pohnert
Max-Planck-Institut für Chemische Ökologie
Carl-Zeiss-Promenade 10
D-07745 Jena
Fax: Internat. code (0)3641-6436-65
e-Mail: Pohnert@ice.mpg.de