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Hypervalent Iodine Compounds

A Versatile and Highly Reactive Polyfluorinated Hypervalent Iodine(III) Compound**

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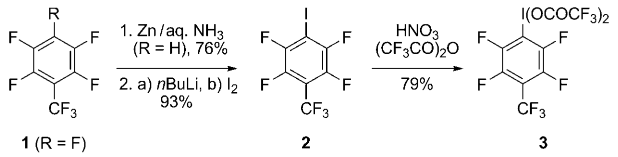
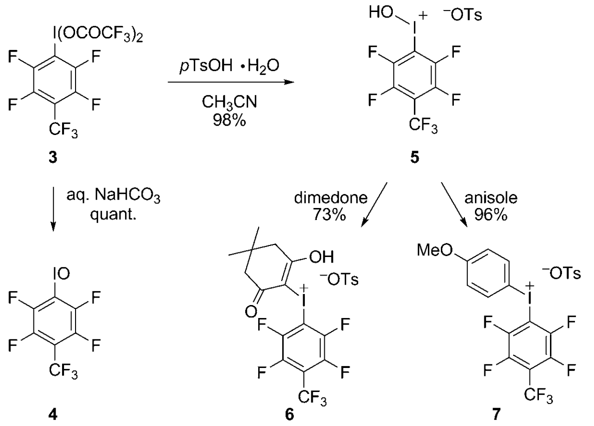
Hypervalent iodine compounds[1] are frequently used reagents that have found wide application in synthesis.[2] They are used in a wide range of transformations as environmentally friendly, mild, and highly selective electrophilic reagents and oxidants since their application sidesteps the issues of toxicity and the complicated ligands of many transition-metal-based systems commonly used for such processes. The drawback of hypervalent iodine compounds can be their low solubility in commonly used organic solvents[3] as well as their potentially explosive character (sometimes found for hyperveralent iodine(V) compounds).[4] Commonly used hypervalent iodine(III) compounds such as $PhI(OAc)_2$ and $PhI(OCOCF_3)_2$ have only moderate reactivity owing to their lower oxidation state.[5,1a] Because polyfluorinated alkyl-substituted hypervalent iodine compounds[6] and $C_6F_5I(OCOCF_3)_2$[7] show increased reactivity and solubility and are easy to recycle, we recently introduced tetrafluorinated IBA (5,6,7,8-tetrafluoro-1-hydroxybenziodoxol-3-one) and IBX (5,6,7,8-tetrafluoro-1-hydroxy-1-oxobenziodoxol-3-one) derivatives.[8]

Herein we describe the synthesis of a highly reactive, polyfluorinated hypervalent iodine(III) reagent, which is readily accessible from commercially available octafluorotoluene (**1**; Scheme 1). Under basic aqueous conditions, **1** was reduced with zinc.[9] Subsequent treatment with *n*BuLi and iodine gave pure 2,3,5,6-tetrafluoro-4-trifluoromethyliodobenzene (**2**). The subsequent oxidation to the iodine(III) derivative **3** was performed using concentrated nitric acid and trifluoroacetic anhydride.[10] The amount of nitric acid was critical, as an excess led to decomposition. Milder oxidants such as H_2O_2·urea,[11] $NaIO_4$,[12] or *meta*-chloroperbenzoic acid[13] did not generate the iodine(III) derivative **3**.



Scheme 1. Synthesis of the λ^3-perfluorinated compound **3**.

The alkaline hydrolysis of **3** is exothermic and proceeded quantitatively to the corresponding fluorinated λ^3-iodosylarene **4**, which was also slowly generated when **3** was exposed to moisture.[14] The ligand-exchange reaction of **3** with *para*-toluenesulfonic acid (*p*TsOH) in acetonitrile[7b] led to the perfluorinated Koser-type reagent **5**.[15] This colorless solid can be stored at room temperature without any protection from light or moisture (Scheme 2). In the α-oxytosylation reaction of propiophenone, **5** gave the desired product in 58 % yield (see the Supporting Information). Although the pentafluoro-substituted Koser reagent is known, its chemistry has been hardly explored.[16,7b]



Scheme 2. Preparation of the iodosylarene **4**, hydroxy(tosyloxy)iodoarene **5**, and the iodonium salts **6** and **7**.

The reaction of **5** with dimedone formed a stable, colorless but amorphous heptafluoroinated iodonium salt **6**. The reaction with anisole under acidic conditions led to iodonium salt **7** in high yield and purity after crystallization (Scheme 2). Single crystals suitable for X-ray diffraction were obtained (Figure 1).[17] Despite quite different electronic structures in the aromatic moieties, both C–I bonds were found to be 2.11 Å long with a C-I-C angle of 89.3°, which leads to an almost orthogonal alignment of the two aromatic moieties. The intermolecular distance between the iodine atom and one of the oxygens of the SO_3^- moiety is around 2.55 Å, which indicates a secondary interaction between the two atoms.[18]

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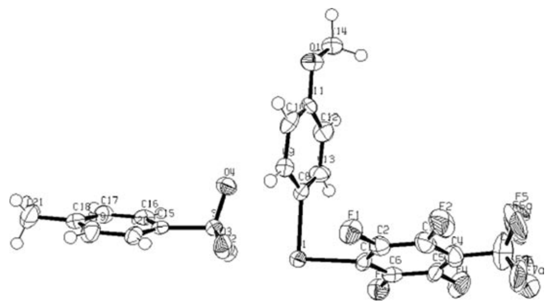
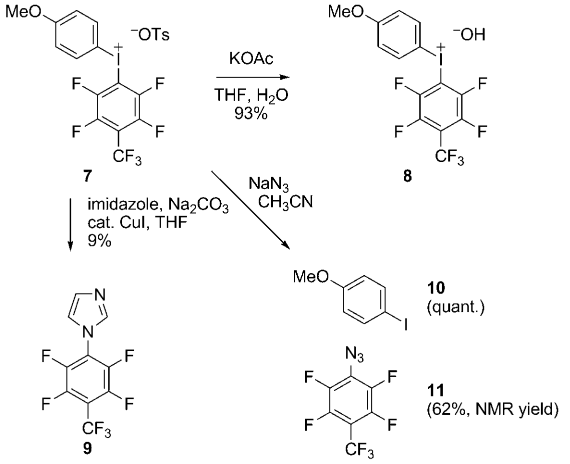


Figure 1. X-ray single-crystal analysis of **7**; ellipsoids at the 70% probability level.

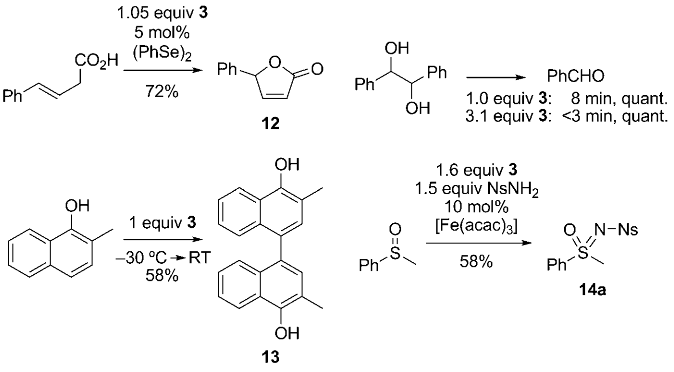
Different reactions of the iodonium salt **7** were investigated. Ligand-exchange reactions leading to **8** proceeded without side reactions, and the stable iodonium species was not attacked under these conditions. However, strong nitrogen nucleophiles can react with **7** to form heptafluorotolyl-substituted compounds, which are highly interesting for the pharmaceutical industry.[19] Whereas imidazole reacted with **7** to give **9** in only low yield in an Ullman-type coupling reaction,[20] azides reacted with **7** to form *para*-iodoanisole (**10**) and *para*-azidoheptafluorotoluene (**11**) quantitatively at elevated temperatures.[21] The NMR spectrum showed complete conversion and *para*-iodoanisole (**10**) was easily to purify, but all efforts to isolate compound **11** failed because it decomposed during column chromatography (Scheme 3).



Scheme 3. Reactions with the iodonium salt **7**.

Some oxidative reactions performed with the new perfluorinated hypervalent iodine(III) reagent **3** are summarized in Scheme 4. The use of **3** in selenium-catalyzed cyclizations[22] leading to **12** is comparable with traditional hypervalent iodine reagents (PhI(OCOCF$_3$)$_2$: 70% yield).

Hypervalent iodine compounds activated by Lewis acids can be used in oxidative aromatic coupling reactions leading to valuable biaryls;[23] in this way toxic and expensive metal reagents can be avoided.[24] Aryl methyl ethers are less problematic as substrates for oxidative aromatic coupling reactions than phenols or naphthols, which readily over-oxidize to quinones.[25] The over-oxidation to the quinone could be avoided by addition of **3** at −30 °C, which facilitated a new oxidative homocoupling of 2-methyl-1-naphthol to give **13** *without* additional Lewis acids (Scheme 4). Dess–Martin periodinane can cleave 1,2-diols, but reagent **3** seems to be superior as hydrobenzoine was cleaved completely to benzaldehyde in only 8 min (with PhI(OCOCF$_3$)$_2$: 20 min). When an excess of reagent **3** (3.1 equiv) was used, the reaction time was less than 3 min and no over-oxidized products were generated.[26]



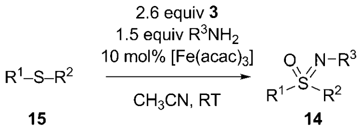
Scheme 4. Reagent **3** as a stoichiometric oxidant in selenium-catalyzed reactions, oxidative homocoupling reactions, and the iron(III)-catalyzed synthesis of sulfoximine **14a**. acac = acetylacetonate.

Sulfoximines are widely used as ligands, auxiliaries, and chiral building blocks.[27] Compound **3** transformed methyl phenyl sulfide to methyl phenyl sulfoxide within 10 min at room temperature without detectable side reactions (with PhI(OCOCF$_3$)$_2$: 15 min). The subsequent oxidation step to the sulfone was slow. Similar syntheses of sulfoxides have already been reported.[28] The sulfoxide can be oxidized by an iron(III)-catalyzed imination to provide sulfoximine **14** (Scheme 4), but other hypervalent iodine reagents can also be used for this reaction.[29]

Sulfoximines **14** can also be synthesized in a single reaction starting from the corresponding sulfides **15**. To the best of our knowledge this is the first example of an iron(III)-catalyzed cascade reaction leading from sulfides directly to sulfoximines using hypervalent iodine(III) reagents as stoichiometric oxidants. Up to now, hypervalent iodine reagents have only been used for the selective oxidation of sulfides to sulfoxides, or, in the presence of amines, from sulfides to sulfilimines.[29,30] The yields of the corresponding sulfoximines **14** were good, but when the slightly less reactive reagent C$_6$F$_5$I(OCOCF$_3$)$_2$ (**16**) was employed, the yield of **14c** dropped to 31% (Table 1, entry 4). The reagent PhI(OCOCF$_3$)$_2$ resulted in similar low yields of **14c** (30%) with increased reaction time, but the remaining sulfide was converted to diphenyl sulfoxide (Table 1, entry 5). With PhI(OAc)$_2$ the main product was the sulfilimine (72%) and only traces of **14c** were observed (Table 1, entry 6). Other examples of this direct transformation using **3** are shown in Table 1.

To compare the reactivity of **3** with that of C$_6$F$_5$I(OCOCF$_3$)$_2$ (**16**) we chose the oxidation of benzyl alcohol to benzaldehyde as a simple test reaction. The reaction was

Table 1: Synthesis of sulfoximines **14** directly from sulfides **15**.

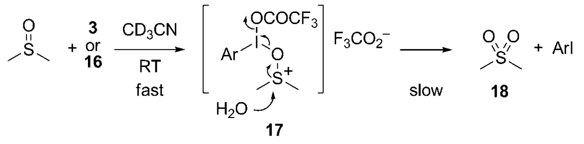


Entry	R^1	R^2	R^3	*t* [h]	Product	Yield [%]
1	Ph	Me	Ns	3	**14a**	42
2	Ph	Me	Ts	3	**14b**	60
3[a]	Ph	Ph	Ns	3	**14c**	51
4[a,b]	Ph	Ph	Ns	3	**14c**	31
5[a,c]	Ph	Ph	Ns	24	**14c**	30[d]
6[a,e]	Ph	Ph	Ns	24	**14c**	trace[f]
7	Ph	Ph	Ts	3	**14d**	50

[a] 1.3 equiv $NsNH_2$ used. [b] Reagent **16** was used instead of **3**. [c] $PhI(OCOCF_3)_2$ was used instead of **3**. [d] The main product is the sulfoxide PhS(O)Ph (70%). [e] $PhI(OAc)_2$ was used instead of **3**. [f] The main product is the sulfilimine PhS(NNs)Ph (72%). Ns = $OSO_2C_6H_4$-4-NO_2, Ts = $OSO_2C_6H_4$-4-CH_3.

performed in an NMR tube at room temperature in deuterated DMSO. Surprisingly we found that the conversion of benzyl alcohol was lower with compound **3** than with $C_6F_5I(OCOCF_3)_2$ (**16**) (see the Supporting Information), probably because **3** reacts with DMSO. As DMSO can be oxidized by hypervalent iodine reagents, the reaction was performed in other solvents. The reaction in CD_3CN and CD_2Cl_2 could not be followed by NMR spectroscopy owing to very broad signals. Therefore the reaction was analyzed by GC–MS, which indicated that **3** is more reactive than **16**. However, the reaction was much slower in acetonitrile, indicating that the hypervalent iodine reagent is activated by coordination to DMSO (see the Supporting Information).

For further insight into this surprising result obtained for the oxidation of benzyl alcohol with **3** and **16**, we investigated their oxidative potential towards DMSO. With a high Gutmann's constant[31] of 29.8 kcal mol^{-1} DMSO was found to act as a ligand for hypervalent iodine(III) compounds. The corresponding complexes **17** are stable at room temperature,[32] and also an X-ray structure for a 1:1 complex of DMSO and $PhIC(SO_2CF_3)_2$ has been published.[33] Residual water will act as a nucleophile and allow the oxidation to proceed (Scheme 5).[28a]



Scheme 5. Oxidation of DMSO by **3** or **16** in CD_3CN.

We have confirmed that DMSO not only acts as a ligand but it is also oxidized by **3** and **16** [and even $PhI(OCOCF_3)_2$] to dimethyl sulfone (**18**) as shown in Scheme 5. Directly after the addition, DMSO coordinates to the hypervalent iodine as evidenced by a shift of the signal for the methyl groups in the ^{1}H NMR spectrum to lower field by $\Delta\delta = 0.20$ ppm. The oxidation of DMSO proceeded faster with **3** than with **16**. The rate constants for the conversion of complex **17** to dimethyl sulfone (**18**) were determined by ^{1}H NMR spectroscopy to be $k(\mathbf{3}) = 0.213\ h^{-1}$ ($\tau_{1/2} = 10$ d); $k(\mathbf{16}) = 0.162\ h^{-1}$ ($\tau_{1/2} = 13$ d); $k(PhI(OCOCF_3)_2) = 0.088\ h^{-1}$ ($\tau_{1/2} = 24$ d) following a linear progression (see the Supporting Information).

The DMSO complex of **3** is a highly reactive oxidant that can oxidize 4-methylanisole to the corresponding benzyl alcohol (9%) and aldehyde (29%) at elevated temperatures. The same reaction performed in CD_3CN gave only traces of oxidation products.

In addition, ligand-transfer reactions to iodobenzene were investigated by ^{1}H NMR spectroscopy. The reaction with **3** to give $PhI(OCOCF_3)_2$ proceeded with 70% conversion and was about 2.4 times faster than the reaction with **16**. This is also in agreement with calculations, which have been performed on these equilibria.[34]

The ligand-exchange reaction between **3**/**16** and iodobenzene was investigated by performing the same reaction in deuterated DMSO instead of CD_3CN. The initial formation of $PhI(OCOCF_3)_2$ was observed until the ^{1}H NMR signals completely disappeared as all these hypervalent iodine compounds reacted with DMSO. For **3**, the maximum conversion (19%) was observed at 205 min. The reaction of reagent **16** with iodobenzene was slower, and the maximum conversion was around 13% after 95 min (Figure 2). As **3** is more electrophilic than **16**, the ligand exchange with iodobenzene is faster and the reaction with DMSO does not dominate.

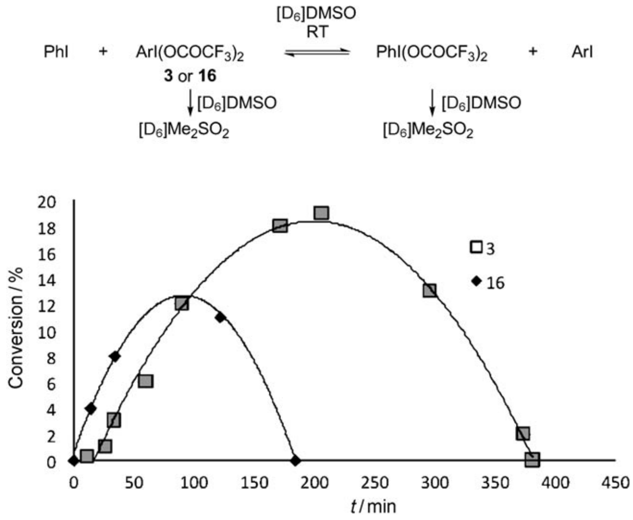


Figure 2. Reaction of iodobenzene with **3** and **16** in [D$_6$]DMSO. See text for details.

We have introduced and explored a new, versatile, and highly reactive polyfluorinated hypervalent iodine(III) compound that is capable of serving as a stoichiometric oxidant in different oxidation reactions such as C–C bond cleavage, the transformation of simple alcohols to aldehydes, and the synthesis of sulfoxides. We also describe the first one-pot synthesis of sulfoximines from sulfides using hypervalent iodine compounds. The new reagent can also perform homocouplings leading to valuable biaryls and can be used as an efficient oxidant in selenium catalysis. Furthermore it can be transformed into several other useful compounds, which then serve in α-oxytosylation reactions and in the introduction of the heptafluorotoluene moiety into N-heterocycles. In simple kinetic studies we showed that λ^3 iodane reagents not only form highly reactive complexes with DMSO which are able to oxidize aromatic side chains, but it can also oxidize DMSO itself. These λ^3 iodine compounds form equilibria in ligand-exchange reactions with iodobenzene. We hope the new compound can serve as a viable alternative when traditional hypervalent iodine (III) reagents fail or give unsatisfactory results.

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