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Tagged Hypervalent Iodine Reagents: A New Purification Concept Based on Ion Exchange through S_N2 Substitution

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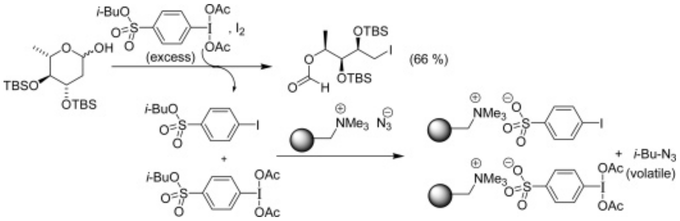
ABSTRACT



The preparation of phenylsulfonate-tagged iodine(III) reagents as well as their use in a novel purification strategy for iodine(III)-promoted reactions is described. The concept is based on ion exchange and is initiated by an azide-promoted S_N2-reaction at the alkyl sulfonate followed by trapping of the resulting aryl sulfonate anion with an ion-exchange resin. The concept is successfully proven for Ru-catalyzed oxidations of alcohols, the activation and glycosidation of thioglycosides, and the Suárez reaction of pyranoses.

The chemistry of hypervalent iodine reagents **1** in the oxidation state +3 has flourished for more than two decades due to their rich and diverse oxidative properties.[1] Ionic as well as radical mechanistic pathways have been discussed for iodine(III)-mediated oxidations. Recently, iodine(III) chemistry has been extended to catalytic processes.[2]

Iodobenzene **2** is a common byproduct in these oxidations. It usually has to be removed chromatographically, which often is a cumbersome task. Therefore, the concept of solid-phase bound and perfluoro-tagged reagents[3] was employed to iodine(III) reagents,[4] which allows easy removal of excess of hypervalent iodine reagent **1** as well as of the reduction product **2** (Figure 1).

All of these concepts are based on the covalent attachment of the iodo moiety to the solid phase or tag. Recycling then requires the reoxidation of the immobilized or tagged aryl iodide which is not always a straightforward procedure, particularly in the case of polymeric backbones which can be prone to oxidation. An alternative solid-phase-assisted

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(1) Reviews on hypervalent iodine reagents: (a) Zdhankin, V. V.; Stang P. J. *Chem. Rev.* **2002**, *102*, 2523−2584. (b) Ochiai, M. *Top. Curr. Chem.* **2003**, *224*, 5−68. (c) Prakash O.; Saini, N.; Sharma, P. K. *Synlett*, **1994**, 221−227. (d) Varvoglis, A. *The Chemistry of Polycoordinated Iodine*; VCH: Weinheim, 1992.

(2) Richardson, R. D.; Wirth, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 4402−4404.

(3) (a) Kirschning, A.; Monenschein, H.; Wittenberg, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 650−679. (b) Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3815−4195. (c) Drewry, D. H.; Coe, D. M.; Poon, S. *Med. Res. Rev.* **1999**, *19*, 97−148. (d) Ley, S. V.; Baxendale, I. R. *Nat. Rev. Drug Discovery* **2002**, *1*, 573−586.

(4) Selected examples: (a) Ley, S. V.; Thomas, A. W.; Finch, H. *J. Chem. Soc., Perkin Trans. 1* **1999**, 669−671. (b) Hossain, Md. D.; Kitamura, T. *Synthesis* **2006**, 1253−1256.

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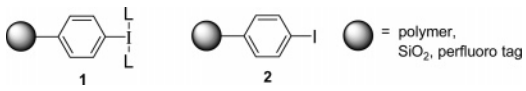
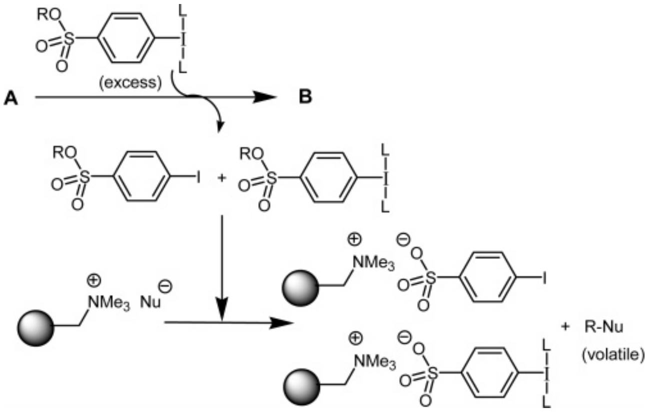


Figure 1. Tagged iodine(III) reagents **1** and corresponding reduction products **2**; L = ligand.

strategy uses scavenger reagents,[3] which so far has hardly found use for iodine(III)-promoted reactions.[5,6] In this paper, we describe a new general scavenging concept, which relies on a sulfonate ester tag acting as a dormant ion-exchange group. The scavenging process is initiated by a S_N2 step which liberates a sulfonate anion. This is directly removed from solution by trapping to an ion-exchange resin. Excess of the tagged reagent is removed likewise by this method. The ion-exchange resin initially serves as a source for the nucleophile that attacks the sulfonate ester. The byproduct R-Nu formed results from the S_N2-displacement and as a consequence ought to be volatile so that it will be removed along with the solvent during workup.

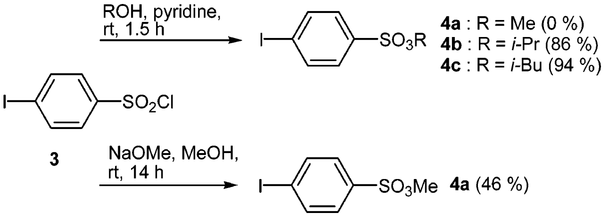
To prove the versatility (efficiency, chemoselectivity) of this concept, we first applied it to several iodine reagents in the oxidation state +3 (Scheme 1). We deliberately chose important or demanding transformations such as the oxidation of alcohols, the oxidative activation of thioglycosides, as well as radical oxidations of carbohydrates (Suárez reaction). The preparation of a set of tagged iodine(III) reagents started from commercially available *p*-iodobenzenesulfonyl chloride **3** (pipsyl chloride) which was converted into the corresponding alkyl sulfonates **4a**−**c** (Scheme 2). Best yields were obtained for isobutyl alcohol in the presence of pyridine. However, conversion strongly depended on the reaction time. While the yield for isobutyl sulfonate **4c** was 94% after 1.5 h it dropped to 80% after a reaction time of 12 h. With isobutyl alcohol as nucleophile the results were likewise and yielded sulfonate **4b**. Prolonged as well as shorter reaction times were completely inadequate for the esterification with methanol. However, methyl sulfonate **4a** could be prepared in moderate yield with an alternative procedure using sodium methanolate and pipsyl chloride **3** in methanol.

Scheme 1. Concept of a Dormant Ion-Exchange Scavenging System[a]



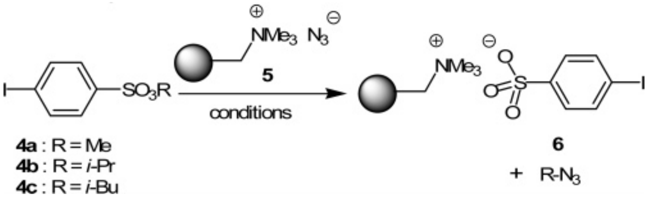
[a] Key: A = starting material; B = product; Nu = nucleophile.

Scheme 2. Preparation of Tagged Iodine(III) Reagents **4a**−**c**



At this early stage, we optimized the scavenging protocol using azide exchange resin **5**. We chose the azide ion because of its good nucleophilic properties. In fact, Hassner and Stern showed that ion-exchange resin **5** can be used for the preparation of alkyl azides from sulfonates.[7] Scavenging was promoted under thermal conditions, and not surprisingly, the reaction time strongly correlated with the size of R (Table 1). While methyl sulfonate **4a** was fully removed from solution at rt within 12 h, isobutyl sulfonate **4c** required 48 h at elevated temperature. MW irradiating conditions dramatically accelerated (1 h) the scavenging process of **4c**. Acetonitrile turned out to be the best solvent for this purpose because of its suitability in S_N2-reactions and its favorable MW absorbing property. In DMF, the process proceeded equally well (1 h, 100 °C, 150 W), but this solvent was abandoned due to its higher boiling point hampering rapid workup.

Table 1. Scavenging of Alkyl Sulfonates **4a**−**c** in Acetonitrile Using Ion-Exchange Resin **5**



entry	R	time	*T* (°C)	yield (%)
1	methyl	24 h	rt	>99
2	isopropyl	24 h	60	>99
3	isobutyl	48 h	60	>99
4	isobutyl	10 min	60 (MW, 150 W)	22
5	isobutyl	3 h	60 (MW, 150 W)	35
6	isobutyl	2 h	100 (MW, 150 W)	>99

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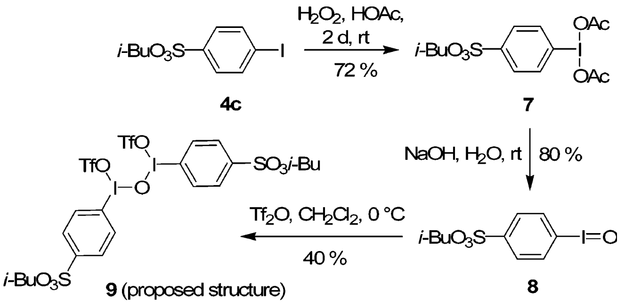
(5) Yusubov, M. S.; Gilmkhanova, M. P.; Zhdankin, V. V.; Kirschning, A. *Synlett* **2007**, 563−566.

(6) Kirschning, A.; Yusubov, M. S.; Yusubova, R. Ya.; Chi, K.-W.; Park, J. Y. *Beilstein J. Org. Chem. (BJOC)* **2007**, *3*.

(7) Hassner, A.; Stern, M. *Angew. Chem.* **1986**, *98*, 479−480; *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 478−479.

Oxidation of the isobutyl 4-iodophenylsulfonate **4c** using the procedure described by Saltzman et al.[8] yielded bis(acetoxy)iodoarene **7** (Scheme 3). Other oxidizing conditions reported (NaBO$_3$,[9] CrO$_3$,[10a] NaIO$_4$,[10b] or K$_2$S$_2$O$_8$[10c]) failed, and in no case were we able to isolate iodanes derived from aryl iodides **4a** and **4b**, respectively.

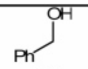
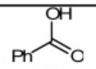
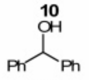
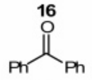
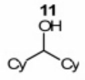
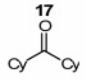
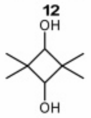
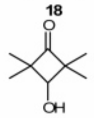
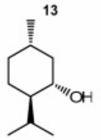
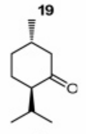
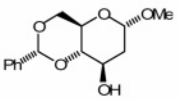
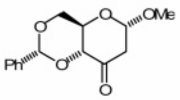
Scheme 3. Preparation of Iodane **7**[11] and Formation of Tagged Iodine(III) Reagents **8** and **9** from **7**



This tagged bis(acetoxy)iodane **7** served as the starting point for the preparation of two other hypervalent iodine reagents containing the dormant sulfonate anion (Scheme 3). However, reaction conditions had to be found which do not result in hydrolysis of the sulfonate group. Saponification of **7** afforded isobutyl iodosylphenylsulfonate **8** in 80% yield. Like iodosylbenzene, derivative **8** is insoluble in organic solvents very likely because of its oligomeric nature. In triflic anhydride, depolymerization proceeds within several minutes to afford a highly labile yellow solid (decomposition to *p*-iodophenylsulfonic acid occurs within a few hours in the glove box) which is expected to be the tagged μ-oxo complex **9**, an analogue of Zefirov's reagent.[12] In principle, other tagged iodine(III) reagents can also be prepared from **7** such as the Koser reagent or alkynyliodonium salts.

Recently, we reported the RuCl$_3$-catalyzed oxidation of alcohols using (diacetoxyiodo)benzene (DIB) as oxidant.[5,13] Evidence was collected that this reaction proceeds via an initial instantaneous Ru-catalyzed disproportionation of DIB to iodobenzene and iodylbenzene with the latter acting as the actual stoichiometric oxidant. We chose this principle reaction to initiate the synthetic evaluation of tagged DIB **7** (Table 2). In principle, oxidations proceeded under similar conditions with similar yields as was shown for DIB.[13] The purification protocol using the azide exchange resin **5** afforded pure oxidation products after filtration and removal of the solvent. In the case of product **18**, contamination with ruthenium was determined to be around 10 ppm as judged by ICP−MS. It can be expected that resin **5** also serves to remove ruthenium salts from the reaction mixture.

Table 2. RuCl$_3$-Catalyzed Oxidation of Alcohols to Carbonyl Compounds Using Tagged DIB **7**

entry	alcohol	time	Product	yield %[a]
1	 **10**	4.0 h	 **16**	95
2	 **11**	2.5 h	 **17**	99
3	 **12**	8 h	 **18**	89
4[b]	 **13**	16 h	 **19**	93
5	 **14**	12 h	 **20**	95
6	 **15**	42 h 28 h	 **21**	32[c] 87[d]

[a] Isolated yield of pure compound. [b] Mixture of diastereoisomers was employed. [c] Method A (Supporting Information), 3.4 equiv of **7**. [d] Method B (Supporting Information), 3.2 equiv of **7**.

As iodine(III) reagents are soft electrophiles, we chose thioglycosides as glycosyl donors in glycosidations.[14] In order to reduce workup to a minimum, not only removal of the iodoarenes has to be guaranteed but also scavenging of other byproducts such as traces of TfOH, thiols, disulfides, and oxygenated disulfides which are formed during the glycosidation process. Fukase and co-workers[15] had demonstrated that efficient activation of thioglycosides can be achieved by using the reagent system iodosylbenzene and triflic anhydride.

As is shown in Scheme 4 a set of reagents was required to cleanly transform 2-deoxy thioglycoside **22** into glycosides **23** and **24**. The optimized procedure (Figure 2) is initiated by first employing the reagent system iodosyl arene/Tf$_2$O

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(8) Sharefkin J. G.; Saltzman, H. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 660; *Org. Synth.* **1963**, *43*, 62.

(9) McKillop, A. Kemp, D. *Tetrahedron* **1989**, *45*, 3299−3306.

(10) (a) Kaźmierczak, P. Skulski, L. *Synthesis* **1998**, 1721−1723. (b) Kaźmierczak, P.; Skulski, L.; Kraszkiewicz, L. *Molecules* **2001**, *6*, 881−891. (c) Hossain, M. D.; Kitamura, T. *Synthesis* **2005**, *12*, 1932−1934.

(11) For details, see the Supporting Information.

(12) Zefirov, N. S.; Zhdankin, V. V.; Dan'kov, V. V.; Koz'min, A. S. *J. Org. Chem. USSR (Engl. Transl.)* **1984**, *20*, 401−403.

(13) Yusubov, M. S.; Chi, K.-W.; Park, J. Y.; Karimov, R.; Zhdankin, V. V. *Tetrahedron Lett.* **2006**, *47*, 6305−6308.

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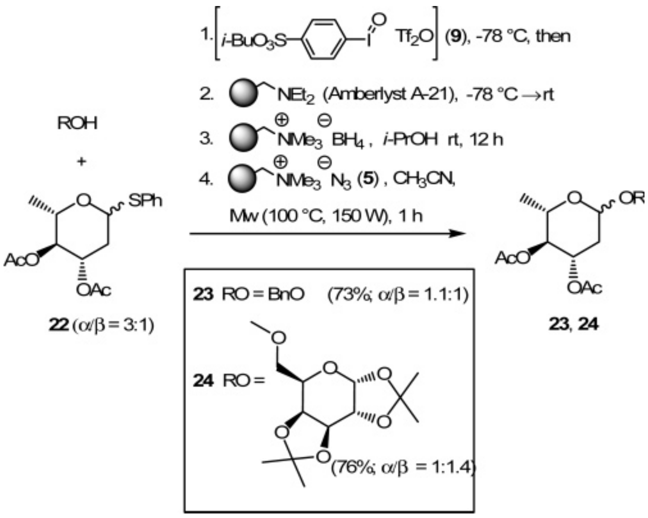
(15) Fukase, K.; Kinoshita, I.; Kanoh, T.; Nakai, Y.; Hasuoka, A.; Kusumoto, S. *Tetrahedron* **1996**, *52*, 3897−3904.

Scheme 4. Iodine(III)-Promoted Glycosidations of Thioglycosides and Scavenging Protocol



which serves to promote glycosidation by electrophilic attack of the iodine(III) species onto the sulfide moiety. Addition of Amberlyst A-21 removes traces of acidic byproducts, while borohydride exchange resin[16] in 2-propanol is very effective in removing all thio-based byproducts.[17] Finally, all sulfonate tagged iodine species are scavenged by the azido exchange resin **5** under microwave irradiation conditions to yield the glycosidation products **23** and **24**, respectively.

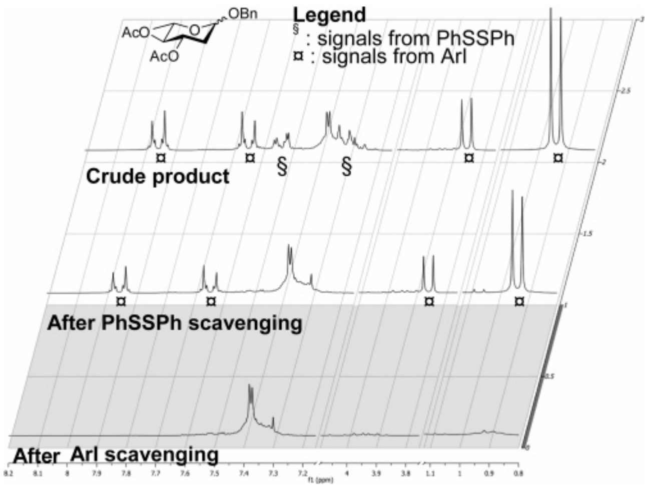
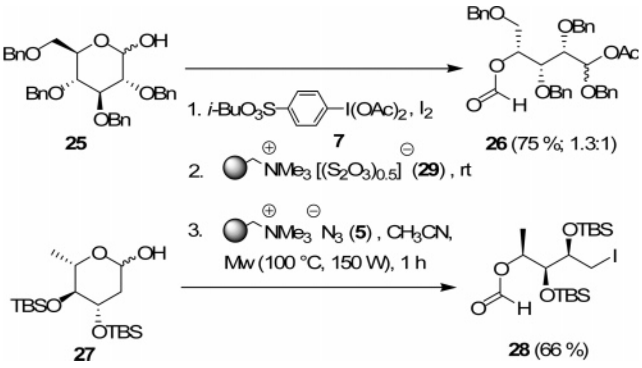


Figure 2. ^{1}H NMR spectra of crude glycosidation product **23** and after sequential treatment with scavinging resins.

Finally, we chose a radical transformation promoted by iodine(III) reagents for which the β-fragmentation of hemiacetalic pyranoses (Suárez reaction)[18] is a very illustrative example (Scheme 5). Here, we chose tagged bis(acetoxy)iodoarene **7** as hypervalent iodine reagent. Thus, pyranoses **25** and **27** in the presence of molecular iodine and **7** afforded formiates **26** and **28**, respectively, after a scavenging protocol which consisted of treatment with thiosulfate exchange resin **29** for removal of the remaining iodine and azide exchange resin **5** under microwave accelerating conditions. Remarkably, formation of the alkyl azide derived from **28** was not observed.

Scheme 5. Radical β-Fragmentation of Pyranoses



In conclusion, we introduced a new concept for scavenging aryliodo species which result as byproducts from iodine(III)-promoted transformations. In principle, the isobutylsulfonyl tag and this scavenging concept are expected to be of general applicability for purification protocols of reagents as well as catalysts. Importantly, scavenging exclusivley relies on ion exchange resins, which allows easy regeneration by simply washing protocols. We believe that it should be possible to implement the concept descibed in continuous flow reactors, as was recently demonstrated for tagged phosphine reagents.[19]

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Supporting Information Available: Descriptions of experimental procedures for compounds and analytical characterization including the X-ray structural analysis of **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[16] Kirschning, A. *J. Prakt. Chem.* **2000**, *342*, 508−511.

[17] (a) Jaunzems, J.; Hofer, E.; Jesberger, M.; Sourkouni-Argirusi, G.; Kirschning, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1166−1170. (b) Jaunzems, J.; Sourkouni-Argirusi, G.; Jesberger, M.; Kirschning, A. *Tetrahedron Lett.* **2003**, *44*, 637−639.

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