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Facile Synthesis of Koser's Reagent and Derivatives from Iodine or Aryl Iodides

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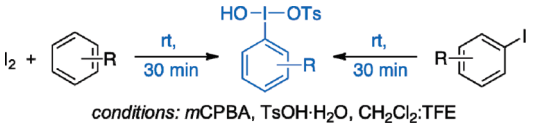
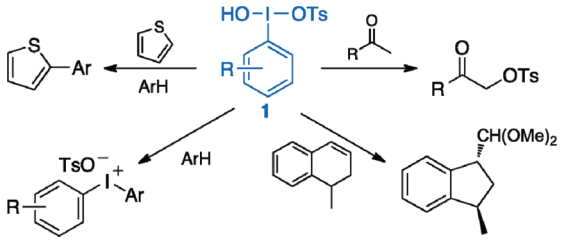


The first one-pot synthesis of neutral and electron-rich [hydroxy(tosyloxy)iodo]arenes (HTIBs) from iodine and arenes is presented, thereby avoiding the need for expensive iodine(III) precursors. A large set of HTIBs, including a polyfluorinated analogue, can be obtained from the corresponding aryl iodide under the same conditions. The reaction proceeds under mild conditions, without excess reagents, and is fast and high-yielding. Together, the two presented routes give access to a wide range of HTIBs, which are useful reagents in a variety of synthetic transformations.

Hypervalent iodine reagents have recently found extensive use as mild oxidants in organic synthesis.[1−3] Iodine(III) compounds like (diacetoxyiodo)benzene and [hydroxy(tosyloxy)iodo]benzene (HTIB, Koser's reagent) are employed in a wide range of transformations, including oxidation of olefins, ring contractions and expansions, dearomatization of phenols, synthesis of iodonium salts, and α-oxidation of carbonyl compounds (Scheme 1).[1,4−8]

SCHEME 1. Applications of HTIBs in Organic Synthesis



α-Tosyloxy ketones are important synthetic intermediates in the synthesis of heterocycles, enediynes, and natural products.[9,10] Recently, the use of chiral HTIBs has been reported, as well as catalytic applications.[11−13]

Substituted versions of HTIB (i.e., [hydroxy(tosyloxy)iodo]arenes **1**) and perfluorinated analogues are useful to vary the reactivity of the reagent[14−16] and to synthesize substituted diaryliodonium[17−22] and alkynyl(aryl)iodonium salts.[23,24]

Synthetic routes to [hydroxy(tosyloxy)iodo]arenes usually consist of two steps, with initial oxidation of an iodoarene to give the corresponding (diacetoxyiodo)arene or a similar iodine(III) species, and subsequent treatment with *p*-toluenesulfonic acid (TsOH) to give the target compound.[1] Togo and co-workers recently reported a one-pot synthesis, where iodoarenes were treated with *m*-chloroperbenzoic acid (*m*CPBA) at room temperature in chloroform to give HTIBs in high yields.[25] The same group has also reported the catalytic formation of HTIBs, using similar conditions, in α-tosyloxylation of carbonyl compounds.[12,13] Another one-pot protocol involves the oxidant Selectfluor.[26]

During our ongoing investigations into efficient one-pot routes to iodonium salts,[27−33] we have found conditions that allow fast and efficient synthesis of Koser's reagent, and

(1) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299–5358.
(2) Varvoglis, A. *Hypervalent Iodine in Organic Synthesis*; Academic Press: San Diego, CA,1997.
(3) *Hypervalent Iodine Chemistry*; Wirth, T., Ed.; Springer: Berlin, Germany, 2003.
(4) Merritt, E. A.; Olofsson, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9052–9070.
(5) Koser, G. F. *Aldrichim. Acta* **2001**, *34*, 89–102.
(6) Moriarty, R. M.; Vaid, R. K.; Koser, G. F. *Synlett* **1990**, 365–383.
(7) Kita, Y.; Morimoto, K.; Ito, M.; Ogawa, C.; Goto, A.; Dohi, T. *J. Am. Chem. Soc.* **2009**, *131*, 1668–1669.
(8) Silva, L. F., Jr. *Molecules* **2006**, *11*, 421–434.
(9) Nicolaou, K. C.; Montagnon, T.; Ulven, T.; Baran, P. S.; Zhong, Y. L.; Sarabia, F. *J. Am. Chem. Soc.* **2002**, *124*, 5718–5728.
(10) Rebrovic, L.; Koser, G. F. *J. Org. Chem.* **1984**, *49*, 2462–2472.
(11) Altermann, S. M.; Richardson, R. D.; Page, T. K.; Schmidt, R. K.; Holland, E.; Mohammed, U.; Paradine, S. M.; French, A. N.; Richter, C.; Bahar, A. M.; Witulski, B.; Wirth, T. *Eur. J. Org. Chem.* **2008**, 5315–5328.
(12) Yamamoto, Y.; Togo, H. *Synlett* **2006**, 798–800.
(13) Tanaka, A.; Togo, H. *Synlett* **2009**, 3360–3364.
(14) Nabana, T.; Togo, H. *J. Org. Chem.* **2002**, *67*, 4362–4365.
(15) Zhdankin, V. V.; Kuehl, C. J.; Simonsen, A. J. *J. Org. Chem.* **1996**, *61*, 8272–8276.
(16) Zagulyaeva, A. A.; Yusubov, M. S.; Zhdankin, V. V. *J. Org. Chem.* **2010**, *75*, 2119–2122.
(17) Ito, M.; Ogawa, C.; Yamaoka, N.; Fujioka, H.; Dohi, T.; Kita, Y. *Molecules* **2010**, *15*, 1918–1931.
(18) Dohi, T.; Ito, M.; Morimoto, K.; Minamitsuji, Y.; Takenaga, N.; Kita, Y. *Chem. Commun.* **2007**, 4152–4154.
(19) Dohi, T.; Yamaoka, N.; Kita, Y. *Tetrahedron* **2010**, *66*, 5775–5785.
(20) Margida, A. J.; Koser, G. F. *J. Org. Chem.* **1984**, *49*, 3643–3646.
(21) Koser, G. F.; Wettach, R. H.; Smith, C. S. *J. Org. Chem.* **1980**, *45*, 1543–1544.
(22) Carroll, M. A.; Pike, V. W.; Widdowson, D. A. *Tetrahedron Lett.* **2000**, *41*, 5393–5396.
(23) Rebrovic, L.; Koser, G. F. *J. Org. Chem.* **1984**, *49*, 4700–4702.
(24) Zhdankin, V. V.; Stang, P. J. *Tetrahedron* **1998**, *54*, 10927–10966.
(25) Yamamoto, Y.; Togo, H. *Synlett* **2005**, 2486–2488.
(26) Ye, C.; Twamley, B.; Shreeve, J. M. *Org. Lett.* **2005**, *7*, 3961–3964.
(27) Bielawski, M.; Olofsson, B. *Chem. Commun.* **2007**, 2521–2523.
(28) Bielawski, M.; Zhu, M.; Olofsson, B. *Adv. Synth. Catal.* **2007**, *349*, 2610–2618.
(29) Zhu, M.; Jalalian, N.; Olofsson, B. *Synlett* **2008**, 592–596.
(30) Bielawski, M.; Aili, D.; Olofsson, B. *J. Org. Chem.* **2008**, *73*, 4602–4607.

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derivatives, from simple and inexpensive arenes. To the best of our knowledge, this is the first report on the synthesis of HTIBs directly from iodine and arenes,[34] thereby avoiding the need for expensive aryl iodides, two-step processes, and long reaction times.

Recent developments in the synthesis of hypervalent iodine compounds involve the use of 2,2,2-trifluoroethanol (TFE) and similar fluorinated solvents.[35,36] Enhanced reactivity and new reaction pathways are often observed in these solvents, the beneficial effects of which are suggested to originate from stabilization of cationic and radical intermediates.[17,19,37]

Kita and co-workers reported the use of fluoroalcohols in the synthesis of diaryliodonium salts,[17−19] and we have subsequently used TFE as cosolvent in our one-pot synthesis of diaryliodonium tosylates from arenes and iodine or iodoarenes.[29] We noticed an enhanced reaction rate also in the formation of Koser's reagent when the oxidation of iodoarenes was with *m*CPBA conducted in a mixture of dichloromethane and TFE. Under these conditions, HTIB (**1a**) was formed in excellent yield in only 15 min at room temperature (Table 1, entry 1). The reaction was easily scaled up to 10 mmol (entry 2), and the yield could be further improved by allowing 30 min reaction time (entry 3). These results should be compared to the 2 h reaction time needed in chloroform.[25]

The scope of this reaction was screened with substituted iodoarenes. Electron-deficient derivatives of HTIBs show enhanced reactivity in oxidation reactions and are therefore of synthetic interest. As electron-rich HTIBs can be used in the synthesis of iodonium salts, iodoarenes with both types of substituents were evaluated in the reaction.

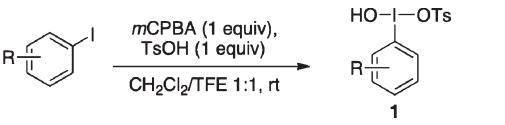
Substrates with a methyl substituent in the ortho or para position gave high yields of **1b** and **1c**, respectively (entries 4 and 5). More electron rich aryl iodides, such as 4-methoxyiodobenzene, were too reactive and gave black mixtures with byproduct formation. Gratifyingly, product **1d** could be obtained in good yield simply by avoiding TFE as cosolvent (entry 6). As previously reported, this compound is unstable and decomposes under vacuum or on storage.[38]

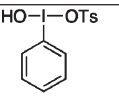
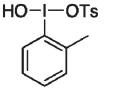
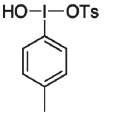
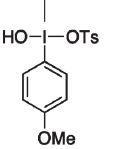
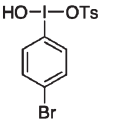
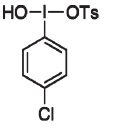
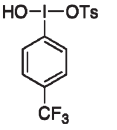
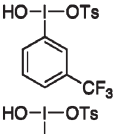
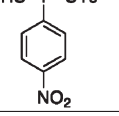
The performance of electron-deficient iodoarenes was then investigated. Halo-substituted substrates were efficiently converted to products **1e**,**f** (entries 7 and 8). As expected, strongly electron-withdrawing substituents, such as trifluoromethyl, resulted in decreased reactivity. Still, product **1g** was obtained in good yield when a longer reaction time was allowed (entries 9−11). Alternatively, a reaction temperature of 40 °C delivered **1g** within 30 min (entry 12). *m*-Trifluoromethyl and *p*-nitro-substituted aryl iodides could also be employed (entries 13−15).

Even the polyfluorinated analogue **2** could be obtained directly from trifluoroethyl iodide (Scheme 2). Although a long reaction time was required for this transformation, it represents the first direct synthesis of a [hydroxy(tosyloxy)iodo]polyfluoroalkane. These interesting compounds have previously been obtained from the corresponding (diacetoxyiodo) or bis(trifluoroacetoxy)iodo derivatives, the synthesis of which require 24−48 h of reaction time.[15,16]

We subsequently investigated the preparation of HTIBs **1** directly from iodine and arenes. These are the expected intermediates in our synthesis of diaryliodonium tosylates

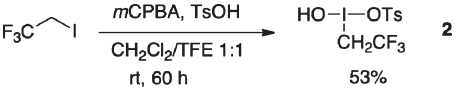
TABLE 1. Synthesis of Substituted HTIBs from Iodoarenes[a]



Entry	Time (min)		Product 1	Yield (%)[b]
1	15	**1a**		89
2[c]	15	**1a**		88
3	30	**1a**		94
4	30	**1b**		87
5	30	**1c**		95
6[d]	30	**1d**		76
7	30	**1e**		91
8	30	**1f**		91
9	30	**1g**		65
10	60	**1g**		76
11	120	**1g**		83
12[e]	30	**1g**		87
13	120	**1h**		72
14[e]	30	**1h**		80
15[e]	30	**1i**		57

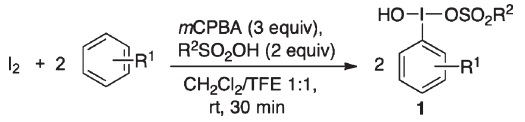
[a]The reactions were performed on 0.10 mmol scale in CH_2Cl_2 (0.5 mL) and TFE (0.5 mL). [b]Isolated yields. [c]10.0 mmol scale. [d]The reaction was performed in CH_2Cl_2. [e]Performed at 40 °C.

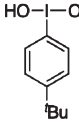
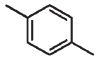
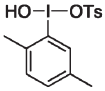
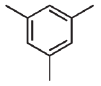
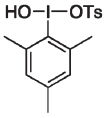
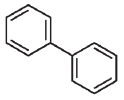
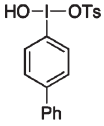
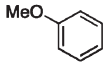
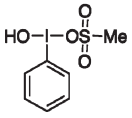
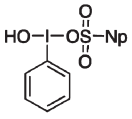
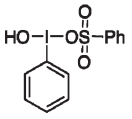
SCHEME 2. Direct Synthesis of Polyfluorinated Analogue 2



(31) Merritt, E. A.; Malmgren, J.; Klinke, F. J.; Olofsson, B. *Synlett* **2009**, 2277–2280.
(32) Jalalian, N.; Olofsson, B. *Tetrahedron* **2010**, *66*, 5793–5800.
(33) Bielawski, M.; Olofsson, B. *Org. Synth.* **2009**, *86*, 308–314.
(34) The direct synthesis of other iodine(III) compounds from iodine and arenes has been reported, see refs 27−29 and the following: (a) Hossain, M. D.; Kitamura, T. *Tetrahedron Lett.* **2006**, *47*, 7889–7891. (b) Hossain, M. D.; Kitamura, T. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 2213–2219.
(35) Dohi, T.; Maruyama, A.; Minamitsuji, Y.; Takenaga, N.; Kita, Y. *Chem. Commun.* **2007**, 1224–1226.
(36) Dohi, T.; Ito, M.; Yamaoka, N.; Morimoto, K.; Fujioka, H.; Kita, Y. *Tetrahedron* **2009**, *65*, 10797–10815.
(37) Dohi, T.; Ito, M.; Yamaoka, N.; Morimoto, K.; Fujioka, H.; Kita, Y. *Angew. Chem., Int. Ed.* **2010**, *49*, 3334–3337.
(38) Papoutsi, I.; Spyroudis, S.; Varvoglis, A.; Raptopoulou, C. P. *Tetrahedron* **1997**, *53*, 6097–6112.

TABLE 2. Synthesis of HTIBs 1 from Iodine, Arenes, and Sulfonic Acids



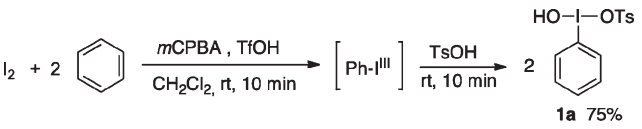
Entry	Arene	Product 1	Yield (%)[a]
1		**1c : 1b** 6:1	73
2		**1j** 	85
3[b]		**1k** 	67
4[b,c]		**1l** 	67[d]
5		**1m** 	23
6[c,e]		**1d**	78
7		**1n** 	76
8		**1o**[f] 	71
9		**1p** 	88
10		**1a : 1c** 3:1	60
11		**1c**	84[g]

[a]Isolated yields. [b]Reaction time 60 min. [c]The reaction was performed in CH_2Cl_2. [d]Contains 0.1 equiv of TsOH. [e]4 equiv of *m*CPBA was used. [f]Np = 2-naphthyl. [g]Yield based on the amount of TsOH used.

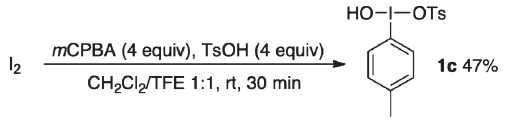
from iodine and arenes with *m*CPBA and tosic acid.[29] Thus, we were aware of the difficulties in iodinating unactivated arenes in the absence of very strong acids, such as trifluoromethanesulfonic acid (TfOH).

Therefore, the reaction was initially examined with use of electron-rich arenes. The reaction conditions were adjusted to allow complete consumption of the iodine by changing the stoichiometry of oxidant and acid. Indeed, treatment of toluene with iodine, *m*CPBA, and TsOH resulted in formation of [hydroxy(tosyloxy)iodo]arenes **1c** and **1b** in a 6:1 ratio (Table 2, entry 1). The regioisomeric mixture of products was expected as the iodination of toluene proceeds with moderate para:ortho selectivity.[27−29]

SCHEME 3. Synthesis of 1a from Iodine and Benzene



SCHEME 4. Formation of Byproduct 1c



tert-Butylbenzene was an excellent substrate, delivering product **1j** as the only regioisomer in 85% yield (entry 2). *p*-Xylene and mesitylene could also be employed, giving **1k** and **1*l***, respectively (entries 3 and 4). Biphenyl was surprisingly unreactive, and prolonged reaction time failed to improve the yield of **1m** (entry 5). Again, *p*-methoxy derivative **1d** was obtained in good yield in the absence of TFE (entry 6).

The acid was subsequently varied using benzene as the arene. Methanesulfonic acid, 2-naphthalenesulfonic acid, and benzenesulfonic acid all delivered the corresponding HTIBs in good yields (entries 7−9), whereas camphorsulfonic acid did not work.[39]

When benzene was reacted with tosic acid, product **1a** was surprisingly obtained as a mixture with byproduct **1c** (entry 10). Furthermore, **1c** was the only observed product in reactions of bromobenzene or chlorobenzene with tosic acid (entry 11). An optimization of the reaction with benzene revealed that **1c** was formed only in the presence of TFE. The oxidation was, however, slow in reactions without TFE, as we have previously experienced for unactivated arenes.[29]

We therefore turned to the use of TfOH, as this should result in rapid formation of an iodine(III) intermediate,[27] which could be converted to Koser's reagent by addition of tosic acid to the reaction mixture. This sequential one-pot procedure proved fruitful, and compound **1a** was cleanly formed in 75% yield (Scheme 3).

This sequential one-pot protocol could be used also in the synthesis of HTIBs from the alkyl-substituted arenes in Table 2, but did not result in better yields compared to the direct reaction with tosic acid.

The formation of byproduct **1c** in reactions with unactivated arenes was intriguing. Indeed, **1c** was formed when iodine was treated with *m*CPBA and TsOH also in the absence of an arene. With the correct stoichiometry of iodine and tosic acid, **1c** was isolated in 47% yield (Scheme 4). The addition of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) as a radical scavenger completely inhibited the reaction, indicating that **1c** is formed from TsOH via a radical mechanism.

To conclude, a fast and efficient synthesis of a wide range of electron-deficient and electron-rich HTIBs **1** from iodoarenes has been developed. The use of TFE as cosolvent increased the reaction rate, resulting in much shorter reaction times than previously reported in oxidations of iodoarenes. A polyfluorinated analogue of Koser's reagent, **2**, has also been synthesized. Furthermore, the direct synthesis of neutral to

(39) The reaction of PhI, *m*CPBA, and CSA according to Table 1 gave the product in 88% yield. Direct formation from PhH and I_2 gave no iodine(III) compound, with the solution remaining purple, indicating that iodination did not proceed.

electron-rich HTIBs from iodine, arenes, and various sulfonic acids has been demonstrated, thereby avoiding the need for expensive iodoarenes. Together, the two presented routes give access to a wide range of [hydroxy(tosyloxy)iodo]-arenes, which are useful reagents in a variety of synthetic transformations.

Experimental Section

General Procedure for the Synthesis of HTIBs 1 from Iodoarenes. To a stirred solution of iodoarene (0.10 mmol) in dichloromethane/TFE (1:1 v/v, 1 mL) was added *m*CPBA (0.10 mmol), followed by $TsOH \cdot H_2O$ (0.10 mmol). The resulting solution was stirred at room temperature for 30 min and concentrated under a stream of air, then diethyl ether (2 mL) was added to the remaining residue. The resulting precipitate was filtered off and dried in vacuo to give compound **1** as a solid.

1-[Hydroxy(tosyloxy)iodo]-4-trifluoromethylbenzene (1g). Colorless solid: mp 146−148 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 8.52 (d, J = 8.4 Hz, 2H), 7.97 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 142.9, 142.0, 137.2, 135.6, 129.9, 129.5, 129.4, 126.9, 124.7 (q, J = 270 Hz), 21.3.

General Procedure for the Synthesis of HTIBs 1 from Iodine and Arenes. Iodine (0.20 mmol) was dissolved in dichloromethane (1 mL) and TFE (1 mL) was added. To the resulting stirred solution was added arene (0.40 mmol), followed by *m*CPBA (0.60 mmol) and $TsOH \cdot H_2O$ (0.40 mmol). The mixture was stirred at room temperature for 30 min. Workup and purification as described above.

1-[Hydroxy(tosyloxy)iodo]-4-*tert*-butylbenzene (1j). Colorless solid: mp 135−137 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 8.27 (dd, J = 6.8, 2.0 Hz, 2H), 7.73 (dd, J = 6.8, 2.0 Hz, 2H), 7.67 (d, J = 6.4, 2.0 Hz, 2H), 7.22 (dd, J = 6.4, 2.0 Hz, 2H), 2.37 (s, 3H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, CD_3OD) δ 159.6, 143.3, 141.8, 138.3, 137.3, 130.1, 129.8, 127.0, 36.5, 31.3, 21.3.

Synthesis of Koser's Reagent (1a) from Iodine and Benzene. To a solution of benzene (36 μL, 0.40 mmol) in dichloromethane (2 mL) were added sequentially iodine (51 mg, 0.20 mmol), *m*CPBA (80% active oxidant, 174 mg, 0.80 mmol), and TfOH (18 μL, 0.20 mmol). The solution was stirred at room temperature for 10 min, then $TsOH \cdot H_2O$ (77 mg, 0.40 mmol) was added. The mixture was stirred for a further 10 min at room temperature and concentrated in vacuo, then diethyl ether (2 mL) was added to the residue. The suspension was stirred at room temperature for 30 min, then filtration afforded the title compound (118 mg, 75%) as a colorless solid. Analytical data were in agreement with the literature.[25]

Synthesis of 1c from Iodine. Iodine (25.0 mg, 0.10 mmol) was dissolved in dichloromethane (0.5 mL) at room temperature and TFE (0.5 mL) was added. To the resulting stirred solution was added *m*CPBA (81% active oxidant, 86 mg, 0.40 mmol), followed by $TsOH \cdot H_2O$ (76 mg, 0.40 mmol). The solution was stirred at room temperature for 30 min and concentrated under a stream of air, then diethyl ether (2 mL) was added to the remaining residue. The suspension was stirred at room temperature for 30 min, then the solid was isolated by filtration and dried in vacuo to give **1c** (38.0 mg, 47%). Analytical data were in agreement with the literature.[26]

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Supporting Information Available: General experimental conditions, analytical data, and ^{1}H and ^{13}C NMRs of products **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.