Novel and efficient synthesis of sulfur-containing heterocycles using a hypervalent iodine(III) reagent

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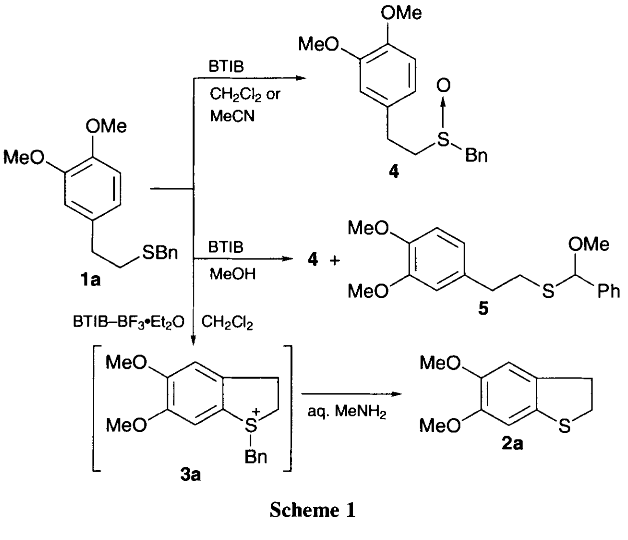
A novel and efficient synthesis of sulfur-containing heterocycles from phenol ethers bearing an alkyl sulfide sidechain using a combined reagent of a hypervalent iodine(III) species and $BF_3 \cdot Et_2O$ is described.

Recently, hypervalent iodine reagents have been extensively used in organic syntheses due to their low toxicity, ready availability and easy handling. As a continuation of our studies concerning hypervalent iodine(III) chemistry,[1] we have developed several inter- and intra-molecular reactions of electron-rich aromatic compounds with some nucleophiles in the presence of [bis(trifluoroacetoxy)iodo]benzene (BTIB) to give synthetically useful products.[2] We report here a novel and efficient synthesis of sulfur-containing heterocycles **2** from phenol ethers **1** bearing an alkyl sulfide sidechain using the combined reagent, BTIB-$BF_3 \cdot Et_2O$, in high yields.

In our previous papers the direct sulfenylation of phenol ethers using BTIB was described.[2e,f] Attempts to apply the methodology to the intramolecular reaction have been made. However, the reaction of the phenol ether bearing a alkanethiol sidechain with BTIB in $(CF_3)_2CHOH$ gave a complex mixture, probably due to the high reactivity of the SH group towards BTIB.[3] Therefore, in order to obtain sulfur-containing heterocycles, we examined phenol ethers **1** bearing an alkyl sulfide sidechain, which were easily prepared from the corresponding iodides by a known method.[4] The treatment of **1a** with BTIB in CH_2Cl_2 or MeCN gave the sulfoxide **4**[5] as a major product, while treatment with BTIB in MeOH gave **4** and the Pummerer-type product **5**,[6] which means that oxidation of the sulfur atom occurs prior to that of the electron rich aromatic ring under these ionic reaction conditions.

On the other hand, the intramolecular cyclization specifically proceeded to give the corresponding sulfur-containing heterocycles in 74–98% yield using BTIB in $(CF_3)_2CHOH$,[2b,d] BTIB–$BF_3 \cdot Et_2O$ in CH_2Cl_2[2e] and BTIB–Me_3SiOTf in CF_3CH_2OH.[2f] Under these conditions no sulfoxides and Pummerer-type products were obtained (Scheme 1).



Scheme 1

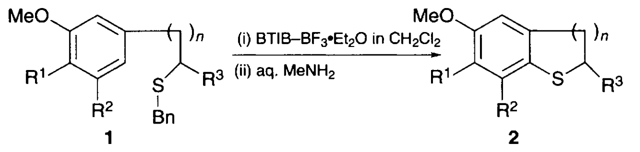
The present method is a rare example which enables control of reactions between two reactive sites using the activated hypervalent iodine species or the special solvent, $(CF_3)_2CHOH$.

The use of a combined reagent BTIB–$BF_3 \cdot Et_2O$ in CH_2Cl_2 is the most useful method for the preparation of sulfur-containing heterocycles **2**† and the results are listed in Table 1.‡

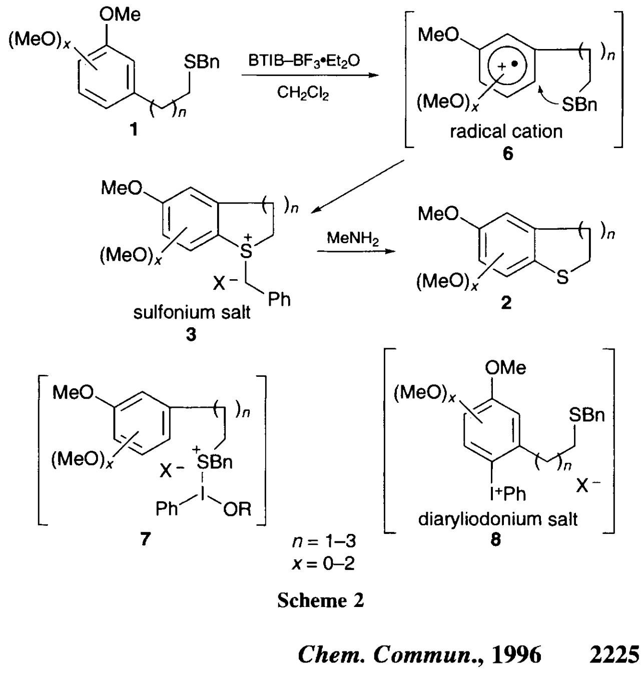
The present method is applicable to substrates having not only mono-, di- and tri-methoxy groups on the aromatic ring but also 2, 3 and 4 carbon sidechains, leading to the corresponding oxygenated hydrobenzothiophenes, hydrobenzothiopyrans and hydrobenzothiepine in fair to excellent yields.

A plausible reaction mechanism is proposed in Scheme 2 based on experimental results§ from intermolecular reactions.

Table 1 Intramolecular cyclization of substituted phenol ethers bearing an alkyl sulfide sidechain with BTIB–$BF_3 \cdot Et_2O$



Entry	Substrate	*n*	R¹	R²	R³	Product	Yield (%)
1	**1a**	1	MeO	H	H	**2a**	98
2	**1b**	2	MeO	H	H	**2b**	89
3	**1c**	3	MeO	H	H	**2c**	53
4	**1d**	2	MeO	H	Me	**2d**	93
5	**1e**	1	H	H	H	**2e**	98
6	**1f**	2	H	H	H	**2f**	93
7	**1g**	1	MeO	MeO	H	**2g**	96
8	**1h**	2	MeO	MeO	H	**2h**	81



Scheme 2

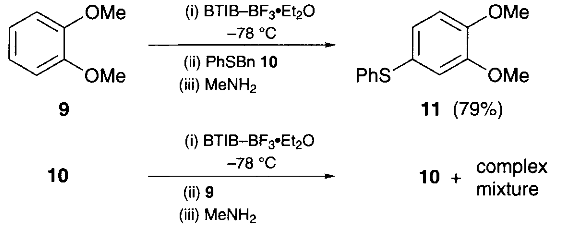
The electron-rich aromatic ring is initially oxidized by the activated hypervalent iodine species *via* single electron transfer (SET), then the sulfide sidechain attacks the radical cation **6** to exclusively form the isolable and stable sulfonium salt **3**. However, other mechanisms *via* the iodonium sulfonium salt **7**[5] or *via* the diaryliodonium salt **8**¶ could also be possible. The benzyl group was easily cleaved by treatment with $MeNH_2$[7] to give the corresponding sulfur-containing heterocycles. The reaction also exclusively gave the corresponding methyl sulfonium salts when methyl sulfides were used as substrates instead of using benzyl sulfides. However, so far, the demethylation has not proceeded in high yields.

Footnotes

† *Preparation* of **2a**: To a stirred solution of **1a** (29.8 mg, 0.103 mmol) in CH_2Cl_2 (3.0 cm^3) was added dropwise a solution of the mixture of BTIB (53.3 mg, 0.124 mmol) and $BF_3{\cdot}Et_2O$ (0.030 cm^3, 0.248 mmol) in CH_2Cl_2 (2.0 cm^3) at −78 °C under a nitrogen atmosphere. The reaction mixture was stirred for 20 min, quenched with 40% $MeNH_2$ solution, then stirred for 30 min and acidified with 10% HCl. The resulting mixture was extracted with CH_2Cl_2, washed with brine, dried, evaporated and purified by preparative TLC (hexane–AcOEt, 5:1) to give **2a** (19.9 mg, 0.101 mmol) in 98% yield.

‡ All compounds were characterized by ^1H NMR spectroscopy and mass spectral analysis.

§ The reaction of *o*-dimethoxybenzene **9** with $BTIB–BF_3{\cdot}Et_2O$ followed by the addition of benzyl phenyl sulfide **10** at −78 °C and then the treatment with $MeNH_2$ gave the corresponding sulfide **11** in 79% yield, while the reaction of **10** with $BTIB–BF_3{\cdot}Et_2O$ followed by the addition of **9** and then the treatment with $MeNH_2$ gave **10** (42%) and a complex mixture, which means that **9** is more reactive than **10** under the stated conditions and also the former reaction gave the same result as the present intramolecular reaction.



¶ In fact, the mechanism *via* **8** is quite possible, however, the nucleophilic attack of the sulfide group on the diaryliodonium salt requires high temperature (220–230 °C) and/or Cu catalyst (120–140 °C) as previously reported (ref. 8).

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