A novel and direct α-azidation of cyclic sulfides using a hypervalent iodine(III) reagent

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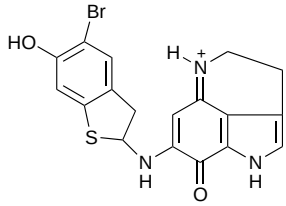
A novel and direct α-azidation of cyclic sulfides using a hypervalent iodine(III) reagent in the presence of Me_3SiN_3 is described; the present method is applicable to substrates which are easily aromatized under oxidative conditions.

α-Azido sulfides have attracted much attention because of their interesting reactivities under various conditions (*e.g.* photochemical, thermal, and other conditions[1]) and their utility as amino cation equivalents.[2] Furthermore, α-azido sulfides have potential for the synthesis of various *N*,*S*-acetals, since the azido moiety can be changed to other aza substituents *via* PPh_3 and catalytic hydrogenation.[3] Generally, *N*,*S*-acetals[4] are difficult to synthesize because of their instability. However, several methods have appeared for the syntheses of *N*,*S*-acetals, *e.g.* addition of thionucleophiles to imine intermediates[5] and addition of aza nucleophiles to thionium intermediates.[6] However, most of the methods have problems in terms of yield and vigorous reaction conditions. Hence, subsequent to the first report[7] by Böhme and Morf, acyclic α-azido sulfides have usually been synthesized stepwise,[1,8] *via* halogenation followed by azidation of sulfides, or *via* thioketals.[9]

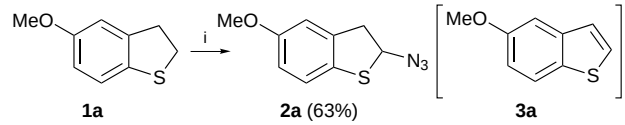
On the other hand, α-azidation of cyclic sulfides, especially dihydrobenzothiophenes, has never been reported, probably due to readily occuring side reactions such as aromatization, sulfoxide formation, benzylic oxidation and α-oxidation of the sulfur atom under oxidative conditions. In particular, α-azidohydrobenzothiophene is thought to be a suitable precursor for the total synthesis of the recently isolated marine anti-cancer alkaloids, discorhabdin A,[10] B,[11] D[12] and makaluvamine F,[13]



Makaluvamine F

whose total syntheses have yet to be accomplished owing to difficulties in constructing their *N*,*S*-acetal skeletons. This prompted us to develop an efficient and general α-azidation method for cyclic sulfides. First, we examined the known stepwise methods to obtain α-azidohydrobenzothiophene. The initial chlorination of **1a** by *N*-chlorosuccinimide (NCS) or SO_2Cl_2,[7,8] however, exclusively gave 5-methoxybenzothiophene **3a**, and oxidation of **1a** to the sulfoxide followed by Pummerer-type azidation gave predominantly **3a** and not **2a**. As part of our continuing studies of hypervalent iodine(III) oxidation,[14] we report here a novel and direct α-azidation method for cyclic sulfides using a combination of PhI=O and Me_3SiN_3 (Scheme 1).

A typical experimental procedure is as follows. To a stirred solution of **1a** in MeCN, Me_3SiN_3 (4.0 equiv.) was added dropwise at −40 °C under nitrogen atmosphere. Iodosylbenzene (2.0 equiv.) was added to the reaction mixture, which was then slowly warmed to −25 °C with stirring for 1–2 h.



1a **2a** (63%) **3a**

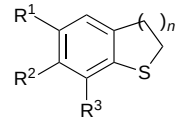
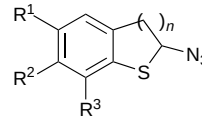
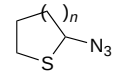
Scheme 1 *Reagents and conditions*: i, PhI=O (2 equiv.), Me_3SiN_3 (4 equiv.), MeCN, −40 to −25 °C

Evaporation of solvent followed by preparative TLC or column chromatography gave **2a** in 63% yield. Of the combination of reagents investigated, PhI=O with Me_3SiN_3 was the best since using $PhI(OCOCF_3)_2$–Me_3SiN_3 or other combined reagents† gave **3a** as the main product. Although the reaction of dihydrobenzothiophene bearing alkoxy substituents with hypervalent iodine(III) reagents has various possibility for (i) α-azidation, (ii) aromatic azidation,[15] (iii) benzylic azidation,[16] (iv) sulfoxide formation,[17] and (v) aromatization to benzothiophene, the present method makes the α-azidation of cyclic sulfides possible predominantly by the use of the combined reagent, PhI=O–Me_3SiN_3. The structure of **2a** was unambiguously established by ^1H NMR, IR and mass spectral and elemental analysis.‡

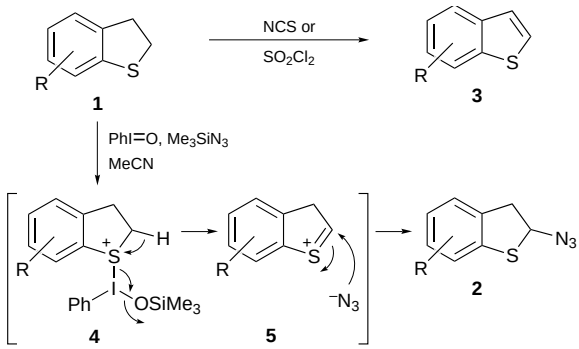
Table 1 shows that the present method is also applicable to mono- and bi-cyclic sulfides **1b**–**i** including dihydrobenzothiophene to give the corresponding α-azido sulfides **2b**–**i** in moderate to good yields. Among the substrates bearing an alkoxy group at the *para* position of the alkyl side chain, benzylic azidation products have also been obtained. In such cases, α-azidation proceeded after protection of the phenolic OH group with an acetyl group (runs 2 and 4).

A plausible reaction mechanism is proposed in Scheme 2. Iodosulfonium cation **4** initially formed from the reaction of

Table 1 α-Azidation of cyclic sulfides using PhI=O–Me_3SiN_3

Entry	Substrate **1**	*n*	R^1	R^2	R^3	Product **2**	Yield (%)
							
1	**1a**	1	OMe	H	H	**2a**	63
2	**1b**	1	H	OAc	H	**2b**	70[a]
3	**1c**	1	OMe	OMe	OMe	**2c**	42
4	**1d**	1	OAc	OAc	H	**2d**	25[a] (67)[b]
5	**1e**	1	H	H	H	**2e**	69
6	**1f**	2	OMe	H	H	**2f**	70
7	**1g**	2	OMe	H	H	**2g**	63
							
8	**1h**	1	—	—	—	**2h**	48
9	**1i**	2	—	—	—	**2i**	62

[a] PhI=O (5.0 equiv.) and Me_3SiN_3 (10.0 equiv.) were used. [b] Yield based on reacted substrate.



Scheme 2

sulfide **1** with PhI=O–Me_3SiN_3, a mechanism well studied by Magnus and co-workers,[18] is then deprotonated to give cation intermediate **5**. Azido anion attack on the α-position of **5** gives the α-azido sulfide **2**. On the other hand, NCS or SO_2Cl_2 causes β-proton abstraction of **5** to give benzothiophene **3** exclusively rather than a nucleophilic attack on the α-carbon. This is probably because the chloride anion is more basic than the Me_3SiO^- anion, generated in the azidation step, and also because Me_3SiO^- is readily neutralized to the siloxane under the reaction conditions used.

In conclusion, a novel and direct α-azidation of cyclic sulfides has been accomplished. This work opens the way to effective syntheses of biologically active natural products carrying *N*,*S*-acetal structures, and provides a direct and efficient method for the synthesis of cyclic α-azido sulfides.

Footnotes and References

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† Other combinations [*e.g.* $PhI(OAc)_2$–NaN_3, *o*-iodobenzoic acid–Me_3SiN_3) were also examined, but only low yields of **2** were obtained.

‡ *Selected data* for **2a**: ν(KBr)/cm^{-1} 2936, 2108, 1597, 1578 and 1473; δ_H (270 MHz, $CDCl_3$) 3.25 (d, 1 H, *J* 16), 3.48 (dd, 1 H, *J* 6, 16), 3.78 (s, 3 H), 5.38 (d, 1 H, *J* 6), 6.78 (d, 1 H, *J* 9), 6.85 (s, 1 H), 7.16 (d, 1 H, *J* 9); δ_C ($CDCl_3$) 44.1, 55.5, 71.0, 111.4, 113.7, 122.9, 128.8, 138.5, 158.1 (Calc. for $C_9H_9N_3OS$: C, 52.16; H, 4.38; N, 20.27; S, 15.47%. Found: C, 52.23; H, 4.43; N, 20.21; S, 15.23%). All newly formed compounds gave satisfactory spectroscopic data.

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