Hypervalent iodine(III) induced intramolecular cyclization of substituted phenol ethers bearing an alkyl azido sidechain–a novel synthesis of quinone imine ketals

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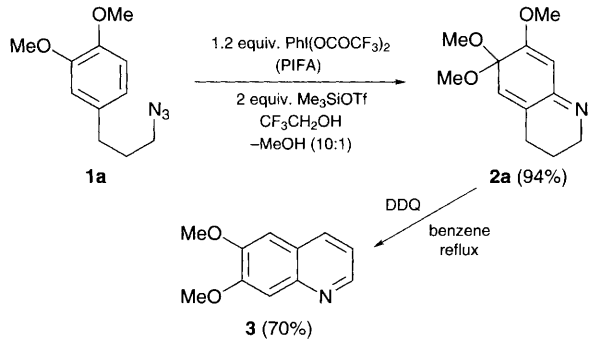
A novel and efficient synthesis of quinone imine ketals from substituted phenol ethers bearing an alkyl azido sidechain using a hypervalent iodine(III) reagent, phenyliodine(III) bis(trifluoroacetate) (PIFA), is described.

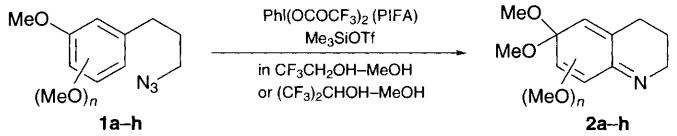
Quinone imines and quinone imine ketals have been proposed as intermediates in a number of biological processes.[1] Quinone imines are also found in the structure of the recently isolated marine alkaloids, amphimedine,[2] cystodytins,[3] diplamine,[4] isobatzellines,[5] wakayin,[6] ascidiidemin[7] and discorhabdins.[8] Because of the unstability of these imines under the conditions used for their formation, only a few preparations have been reported, *e.g.* the anodic oxidation of anilides[9] or 4-methoxyphenol derivatives,[10] the hypervalent iodine oxidation of aniline derivatives,[11] or the mild deprotection of the amino sidechain of *p*-quinones and *p*-quinone monoacetals.[12] As a continuation of our studies concerning hypervalent iodine(III) chemistry,[13] we have recently developed several reactions of electron-rich phenol ethers with phenyliodine(III) bis(trifluoroacetate) (PIFA).[14] Here we report a novel direct preparation of quinone imine ketals from substituted phenol ethers bearing an alkyl azido sidechain using the hypervalent iodine reagent, PIFA, without an imine formation step between the carbonyl group and amino group.

A typical experimental procedure is as follows. To a stirred solution of **1a** in CF_3CH_2OH–MeOH (10:1) was added



Scheme 1

Table 1 Intramolecular cyclization of substituted phenol ethers bearing an alkyl azido sidechain with PIFA



Run	Starting material	Solvent	Product	Yield (%)
1	**1a** R^1, R^2, R^3 = H	CF_3CH_2OH–MeOH	**2a–d**	94
2	**1a** R^1, R^2, R^3 = H	$(CF_3)_2CHOH$–MeOH		86
3	**1b** R^1, R^2 = H, R^3 = Me	CF_3CH_2OH–MeOH		70
4	**1c** R^1 = H, R^2, R^3 = Me	CF_3CH_2OH–MeOH		72
5	**1d** R^1 = Me, R^2, R^3 = H	CF_3CH_2OH–MeOH		85
6	**1e** R^1, R^2, R^3 = H	CF_3CH_2OH–MeOH	**2e–g**	51[a]
7	**1f** R^1= H, R^2, R^3 = Me	CF_3CH_2OH–MeOH		64
8	**1g** R^1 = Me, R^2, R^3 = H	CF_3CH_2OH–MeOH		62
9	**1h**	$(CF_3)_2CHOH$–MeOH	**2h** (27) + **4** (67)	

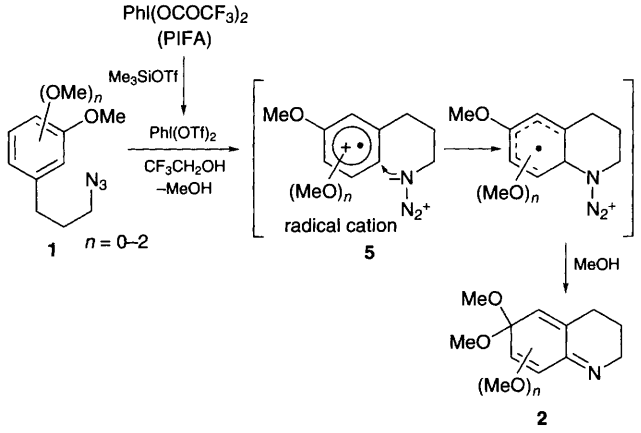
[a] NMR yield of **2e** after work-up is >90%.

dropwise 2.0 equiv. of trimethylsilyl trifluoromethane sulfonate (Me_3SiOTf) at 0 °C under a nitrogen atmosphere. PIFA (1.2 equiv.) was added to the reaction mixture which was then stirred for 30 min. Aqueous work-up with saturated $NaHCO_3$ followed by preparative TLC gave the labile quinone imine ketal **2a** in 94% yield. The structure of **2a** was unambiguously established by ^1H NMR and IR spectroscopy and elemental analysis.† Furthermore, **2a** could be easily converted to the corresponding quinoline **3a** by treatment with DDQ in refluxing benzene for 30 min (Scheme 1). The results are summarized in Table 1.

The cyclization reaction proceeds smoothly in polar and low nucleophilic solvents, such as CF_3CH_2OH and $(CF_3)_2CHOH$ in the presence of 10% MeOH. Quinone imine ketals could not be obtained in other solvents such as CH_2Cl_2, MeCN, MeOH or in the absence of MeOH and Me_3SiOTf. The present method is applicable to substrates having mono- and di-methoxy groups on the aromatic ring and/or methyl groups at the benzylic position or α-position of the azido group. The cyclized product **2h** was obtained in only 27% yield, but **4** was mainly formed in the case of the trimethoxy benzene **1h** probably due to steric hindrance on the aromatic ring.

A plausible reaction mechanism is proposed in Scheme 2. The radical cation **5** is initially formed by the reaction of the electron-rich aromatic ring with hypervalent iodine species activated by Me_3SiOTf as mentioned in our former work,[14c] followed by nucleophilic attack of the azido group, and then deprotonation and removal of nitrogen to give the corresponding quinone imine ketal **2**.

In conclusion, we have developed a novel and direct synthetic method for quinone imine ketals. To our knowledge, this is the first example of the intramolecular cyclization of phenol derivatives using hypervalent iodine reagent by nucleophilic attack of the alkyl azido group instead of the amino and amide groups, which are very reactive to hypervalent iodine species.[15,16]



Scheme 2

Footnote

† *Spectroscopic data* for **2a**: IR (KBr) ν cm^{-1} 2935, 1630, 1585 and 1460, ^1H NMR (200 MHz, $CDCl_3$): δ 1.78 (t, 2 H, *J* 6.5 Hz), 2.51 (t, 2 H, *J* 6.5 Hz), 3.26 (s, 6 H), 3.77 (s, 3 H), 3.81 (t, 2 H, *J* 6.5 Hz), 5.76 (br s, 2 H). All products were characterized by ^1H NMR and IR spectroscopy and mass spectral analysis.

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