Hypervalent Iodine(III)-induced Intramolecular Cyclization Reaction of Substituted Phenol Ethers with an Alkyl Azido Side-chain: A Novel and Efficient Synthesis of Quinone Imine Derivatives

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Received September 11, 1998; accepted October 30, 1998

Novel and efficient syntheses of quinone imine ketals (2a—j) and quinone imines (4a—h) from substituted phenol ethers (1a—k) bearing an alkyl azido side-chain using the combination of hypervalent iodine(III) reagent, phenyliodine(III) bis(trifluoroacetate) (PIFA) and trimethylsilyl trifluoromethanesulfonate (TMSOTf), have been developed.

Key words quinone imine ketal; quinone imine; hypervalent iodine(III) reagent; phenyliodine(III) bis (trifluoroacetate)

Quinone imines and quinone imine monoacetals have been proposed as intermediates in a number of biological processes. Quinone imines are also found in the structure of the recently isolated marine alkaloids, amphimedine,²¹ cystodytins,²¹ diplamines,²¹ isobazellines,²¹ wakayins,²¹ ascididemin,²¹ makaluvamines²¹ and discorhabdins.²¹ Because of the instability of these imines under the conditions required for their formation, only a few preparations have been reported, e.g. the Fremy’s salt oxidation of phenol derivatives,¹⁰ the anodic oxidation of anilides¹⁰ or 4-methoxyphenol derivatives,¹¹ the hypervalent iodine oxidation of aniline derivatives,¹² or the mild deprotection of the amino side-chain of p-quinones and p-quinone monoacetals.¹³ As a continuation of our studies concerning hypervalent iodine(III) chemistry,¹⁴ we have recently developed several reactions of electron-rich phenol ethers with phenyliodine(III) bis(trifluoroacetate) (PIFA).¹⁵ Very recently, we briefly published a novel and efficient synthesis of quinone imine ketals (2) from substituted phenol ethers (1) bearing an alkyl azido side-chain using the combination of hypervalent iodine reagent, PIFA and trimethylsilyl trifluoromethanesulfonate TMSOTf.¹⁶ In this paper, we give a full account of this and additional studies on an efficient direct synthesis of quinone imines (4) from 1.

Results and Discussion

First, we examined the possibility of direct preparation of nitrogen-containing heterocycles using PIFA in (CF₃)₂CHOH or CF₃CH₂OH according to our previously reported intermolecular azidation.¹⁵a,b) The reaction of 1a with PIFA in (CF₃)₂CHOH yielded quinone imine (4a) in poor yield. Activation of PIFA by adding 2.4 eq of TMSOTf in the presence of 10% MeOH was found to give quinone imine ketal (2a) predominantly. The cyclization reaction proceeds smoothly in polar and weakly nucleophilic solvents, such as CF₃CH₂OH (94%) and (CF₃)₂CHOH (86%), in the presence of 10% MeOH to give 2a. 2a could also be obtained in CH₂Cl₂–MeOH (70%) and CH₃CN–MeOH (66%). However, 2a could not be obtained in MeOH or in the absence of MeOH and TMSOTf, but a complex mixture (in MeOH) or quinone imine methyl trifluoroethyl ketal (50% yield, PIFA in CF₃CH₂OH) was obtained. 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 results are summarized in Table 1. Furthermore, other ketals of different alcohols, such as EtOH and ethylene glycol, were also obtained in good yields (Table 1, runs 3, 4). The cyclized product 2 was obtained in only 27% yield, but 3 was mainly formed in the case of the trimethoxybenzene 1h, probably due to steric hindrance involving the aromatic ring (run 11).

Next, we examined the direct synthesis of quinone imines. To begin with, treatment of 1a with PIFA–TMSOTf in CF₃CH₂OH–H₂O gave the corresponding quinone imine (4a) only in poor yield, while by-products, in which the trifluoroethoxy group was introduced, were partly obtained due to the slight nucleophilicity of CF₃CH₂OH. Consequently, the best result was obtained by using CH₂Cl₂–H₂O (50 : 1) to give the corresponding quinone imines (4a—h) in good yields. The purification of 4a—h was performed by flash column chromatography on Al₂O₃ because of the low stability and high polarity, compared with the corresponding quinone imine ketals (2a—j). The results are summarized in Table 2.

A plausible reaction mechanism is proposed in Chart 1. The cation radical (5) is initially formed by reaction of the electron-rich aromatic ring with hypervalent iodine species activated by TMSOTf, as mentioned in our earlier paper,¹⁵b) followed by nucleophilic attack of the azido group, and then deprotonation and removal of nitrogen to give the corresponding quinone imine ketals (2) and quinone imines (4).

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Other mechanisms might be possible such as via a diaryl iodonium salt\(^{17}\) (6) and via an iodoimine intermediate\(^{18}\) (7). However, the iodonium salt (6) is thought to react with only activated nucleophiles as described in our previous report.\(^{17}\) Furthermore, reaction of phenethyl azide with PIFA–TMSOTf did not take place in CF\(_3\)CH\(_2\)OH–MeOH or CH\(_2\)Cl\(_2\)–H\(_2\)O and the starting azide was recovered. Therefore, the phenol ether moiety, rather than the azido group, initially reacted with PIFA–TMSOTf and the cation radical (5) is more likely to be a reactive intermediate than 6. The azido group, which is not very reactive with hypervalent iodine species, plays an important role in the reaction. Thus, the reaction of
phenol ethers bearing an alkyl amino or an amide side-chain with PIFA-TMSOTf sometimes gave a complex mixture, probably due to competitive reactions between the phenol ether moiety and the amine group.

In conclusion, a novel and direct synthesis of quinoline imine ketals (2) and quinoline imines (4) has been developed. This method will provide a powerful tool for the total synthesis of various types of biologically active quinoline imine alkaloids.

Experimental

All melting points are uncorrected. NMR spectra were measured on 200, 270, and 300 MHz spectrometers with CDCl3 as a solvent and SiMe4 as an internal standard. Infrared (IR) absorption spectra were recorded using KBr pellets. E. Merck Silica-gel 60 for column chromatography and E. Merck precoated TLC plates, Silica-gel F254 for preparative thin-layer chromatography (prep. TLC) were used. Organic layers were dried with anhydrous Na2SO4. PIFA is commercially available.

Preparation of Phenol Ethers with an Alkyl Azido Side-chain 1a.e.h

If phenol ethers were prepared from the corresponding methyl phenylpropiionate via 3 steps (1) H2 in tetrahydrofuran (THF), 2) LiPPh2, imidazole in toluene, 3) NaH in N,N-dimethylformamide (DMF) 1b was prepared from 3,4-dimethylphenyl proponic acid chloride via 4 steps (1) AlMe3, Cu(acac)2, PPh3, in THF, 2) NaH in EtOH, 3) LiPPh2, imidazole in toluene, 4) NaH in DMF. 1c.f.i.j.k were prepared from the corresponding methyl phenylpropiionate or methyl phenylacetate via 2 steps (1) MeMgI in Et2O, 2) TMSN3. 2f.d. was prepared from saturated NaHCO3 aq., H2O and brine, and evaporated in vacuo. The residue was purified by column chromatography or preparative TLC on silica-gel to give the corresponding quinoline imine ketal 2.

Synthesis of Quinoline Imines: To a stirred solution of 1 (0.100 mmol) in CF3CH2OH (3 mL)-MeOH (0.3 mL) was added dropwise TMSOTf (0.2 mmol) and PIFA (0.12 mmol), sequentially at 0 °C under nitrogen. The reaction mixture was stirred for 30 min at 0 °C, and then saturated NaHCO3 aq. added at room temperature. The resulting mixture was extracted with CH2Cl2 (10 mL×3); the combined organic layer was washed with saturated NaHCO3 aq., H2O, and brine, and evaporated in vacuo. The residue was purified by column chromatography on neutral alumina to give the corresponding quinoline imine 4.

Several quinoline imine ketals and quinoline imines decomposed during re-crystallization and the measurement of the 13C-NMR spectra was difficult because of their instability.

6.6.7-Trimethoxy-2,3,4,6-tetrahydroquinoline (2a) 1a (29.0 mg, 0.131 mmol) in CF3CH2OH (3 mL)-MeOH (0.3 mL), TMSOTf (0.061 ml, 0.314 mmol), and PIFA (0.676 mg, 0.157 mmol) gave 2a (27.6 mg, 94%) as a colorless crystals, mp 103—108 °C (from n-hexane–Et2O, O). IR (KBrs): 2935, 1630, 1585, 1460 cm−1. 1H-NMR (300 MHz) δ: 1.78 (2H, t, J = 6.0, 5.5 Hz), 2.51 (2H, t, J = 6.0 Hz), 3.25 (6H, s), 3.76 (3H, s), 3.79 (2H, t, J = 5.5 Hz), 5.78 (1H, d, J = 7.9 Hz), 5.97 (1H, d, J = 7.9 Hz). 13C-NMR (75 MHz) δ: 22.8, 27.5, 30.6, 53.9, 55.5, 95.1, 128.4, 128.6, 132.3, 133.9, 136.3, 142.1. HRMS Calcd for C16H15NO: C 74.50, 74.51. Found: 74.50, 74.51. HRMS Calcd for C16H15NO: C 74.50, 74.51. Found: 74.50, 74.51.

6.6-Diethoxy-7-methoxy-2,3,4,6-tetrahydroquinoline (2b) 1a (31.4 mg, 0.142 mmol) in CF3CH2OH (3 mL)-EtOH (0.3 mL), TMSOTf (0.066 ml, 0.341 mmol), and PIFA (73.2 mg, 0.170 mmol) gave 2b (23.1 mg, 65%) as a colorless needles, mp 64 °C (from n-hexane–Et2O, O). IR (KBrs): 2934, 1670, 1625, 1585 cm−1. 1H-NMR (300 MHz) δ: 1.19 (6H, t, J = 10.0 Hz), 2.07—2.10 (2H, m), 2.87—2.90 (4H, m), 3.75 (3H, s), 3.79 (2H, t, J = 5.5 Hz), 5.75 (2H, d, J = 7.9 Hz). 13C-NMR (75 MHz) δ: 15.4, 22.7, 27.3, 50.1, 53.9, 95.4, 104.6, 120.7, 129.0, 158.3, 160.0. HRMS Calcd for C16H15NO: C 75.72, 75.73. Found: 75.72, 75.73.

6.6-Ethynylideneno-2,3,4,6-tetrahydroquinoline (2c) 1a (26.1 mg, 0.118 mmol) in CH2Cl2 (2.5 mL)-HOCH2CH(OH) (0.05 ml), TMSOTf (0.055 ml, 0.285 mmol), PIFA (60.9 mg, 0.142 mmol) gave 2c (21.8 mg, 83%) as a colorless oil. IR (KBrs): 2900, 1675, 1630, 1585 cm−1. 1H-NMR (270 MHz) δ: 1.69—1.79 (2H, m), 2.44—2.46 (2H, m), 2.58—2.60 (2H, m), 3.76 (3H, s), 3.73 (2H, t, J = 5.5 Hz), 5.07—5.10 (2H, m), 5.16—5.18 (2H, m), 5.56 (2H, s), 5.67 (1H, s). 13C-NMR (75 MHz) δ: 22.6, 27.3, 50.3, 55.3, 66.7, 100.2, 102.4, 128.3, 128.6, 158.0, 161.4. HRMS Calcd for C16H15NO: C 75.72, 75.73. Found: 75.72, 75.73.

2-(4,4-Dimethyl-3-(4-methylphenoxy)-2,3-dimethylbutyl)phenol (1j) A colorless oil. IR (KBrs): 2905, 1600, 1585 cm−1. 1H-NMR (250 MHz) δ: 1.15 (3H, s), 1.19 (3H, s), 1.27 (3H, d, J = 6.9 Hz), 1.76 (1H, dd, J = 14.3, 5.0 Hz), 1.91 (1H, d, J = 14.3, 8.0 Hz), 2.81—2.95 (1H, m), 3.86 (3H, s), 3.92 (3H, s), 6.73 (1H, s), 6.74 (1H, d, J = 8.6, 1.7 Hz), 6.80 (1H, d, J = 8.6 Hz). HRMS Calcd for C21H18O2N: 323.1634. Found: 243.1660.

2-(4,4-Dimethyl-3-(4-methylphenoxy)phenyl)-3-methoxybenzene (4c) A colorless oil. IR (KBrs): 2905, 1600, 1585 cm−1. 1H-NMR (200 MHz) δ: 1.26 (3H, s), 3.68 (3H, s), 3.88 (3H, s), 6.70—6.81 (3H, m). HRMS Calcd for C14H18O2N: 235.1231. Found: 235.1232.

General Experimental Procedure

Synthesis of Quinoline Imines: To a stirred solution of 1 (0.100 mmol) in CF3CH2OH (3 mL)-MeOH (0.3 mL) was added dropwise TMSOTf (0.2 mmol) and PIFA (0.12 mmol), sequentially at 0 °C under nitrogen. The reaction mixture was stirred for 30 min at 0 °C, and then saturated NaHCO3 aq. added at room temperature. The resulting mixture was extracted with CH2Cl2 (10 mL×3); the combined organic layer was washed with saturated NaHCO3 aq., H2O, and brine, and evaporated in vacuo. The residue was purified by column chromatography on neutral alumina to give the corresponding quinoline imine 2.

Several quinoline imine ketals and quinoline imines decomposed during re-crystallization and the measurement of the 13C-NMR spectra was difficult because of their instability.
2.2-Dimethyl-6,6,7-trimethoxy-3,4,4-triethynylquinoline (2f) 1c
(17.4 mg, 0.070 mmol) in CH₂(C₂H₅)(2 ml)–MeOH (0.2 ml), TMSOTf (0.032 ml, 0.166 mmol), and PIFA (36.0 mg, 0.084 mmol) gave 2e (12.6 mg, 72%) as a colorless needles, mp 78 °C. IR (KBr): 2940, 1670, 1630, 1580 cm⁻¹. 1H-NMR (270 MHz) δ: 1.26 (6H, s), 1.65 (2H, t, J=6.0 Hz), 2.52 (2H, t, J=6.0 Hz), 3.26 (6H, s), 3.75 (3H, s), 5.76 (1H, s), 5.79 (1H, s). 13C-NMR (67.5 MHz) δ: 23.9, 29.5, 34.1, 51.3, 54.9, 55.5, 95.8, 104.9, 128.1, 130.1, 155.2, 159.0. HRMS Calculated for C₁₁H₁₂NO₂: 251.1520. Found: 251.1520.

4-Methyl-6,6,7-trimethoxy-3,4,4-triethynylquinoline (2f) 1d (30.0 mg, 0.128 mmol) in CH₂(C₂H₅)(3 ml)–MeOH (0.3 ml), TMSOTf (0.059 mmol, 0.353 mmol), and PIFA (65.8 mg, 0.153 mmol) gave 2f (25.8 mg, 85%) as a colorless oil. IR (KBr): 2935, 1670, 1630, 1585 cm⁻¹. 1H-NMR (300 MHz) δ: 1.19 (3H, d, J=7.0 Hz), 1.40—1.54 (1H, m), 1.77—1.88 (1H, m), 2.48—2.52 (2H, t, J=11.0 Hz), 3.23 (2H, t, J=11.0 Hz), 3.75 (3H, s), 3.94 (1H, d, J=18.0, 4.85 Hz), 5.75 (1H, s), 5.83 (1H). 13C-NMR (67.5 MHz) δ: 23.9, 29.5, 34.1, 51.3, 54.9, 55.5, 95.8, 104.9, 128.1, 130.1, 155.2, 159.0. HRMS Calculated for C₁₁H₁₂NO₂: 251.1520. Found: 251.1520.

1H-NMR (270 MHz) δ: 1.24 (3H, d, J=6.6 Hz), 1.50—1.64 (1H, m), 1.84—1.96 (1H, m), 2.60—2.76 (1H, m), 3.79 (3H, s), 3.93 (1H, d, J=20.0, 8.9, 4.3 Hz), 4.24 (1H, dt, J=20.0, 4.5 Hz), 6.24 (1H, s), 6.34 (1H, s). HRMS Calculated for C₁₃H₁₇NO₂: 219.1094. Found: 219.1098.

4-Methyl-3,4,3-dihydro-6(2H)-quinoline (4d) 1d (18.5 mg, 0.079 mmol) in CH₂(C₂H₅)(2 ml)–H₂O (0.04 ml), TMSOTf (0.036 ml, 0.186 mmol), and PIFA (40.6 mg, 0.094 mmol) gave 4d (12.4 mg, 82%) as an unstable solid. IR (KBr): 2975, 1655, 1630, 1595 cm⁻¹. 1H-NMR (270 MHz) δ: 1.24 (3H, d, J=6.6 Hz), 1.50—1.64 (1H, m), 1.84—1.96 (1H, m), 2.60—2.76 (1H, m), 3.79 (3H, s), 3.93 (1H, d, J=20.0, 8.9, 4.3 Hz), 4.24 (1H, dt, J=20.0, 4.5 Hz), 6.24 (1H, s), 6.34 (1H, s). HRMS Calculated for C₁₃H₁₇NO₂: 219.1094. Found: 219.1098.

Acknowledgments This work was supported in part by Grant-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture, Japan.

References and Notes


