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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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.[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] ascididemin,[7] makaluvamines[8] and discorhabdins.[9] 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 anilides[10] 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 trifluoromethane sulfonate 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 $(CF_3)_2CHOH$ or CF_3CH_2OH according to our previously reported intermolecular azidation.[15a,b] The reaction of **1a** with PIFA in $(CF_3)_2CHOH$ 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 CF_3CH_2OH (94%) and $(CF_3)_2CHOH$ (86%), in the presence of 10% MeOH to give **2a**. **2a** could also be obtained in CH_2Cl_2–MeOH (70%) and CH_3CN–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 CF_3CH_2OH) 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 **2j** 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 CF_3CH_2OH–H_2O 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 CF_3CH_2OH. Consequently, the best result was obtained by using CH_2Cl_2–H_2O (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 Al_2O_3 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**).

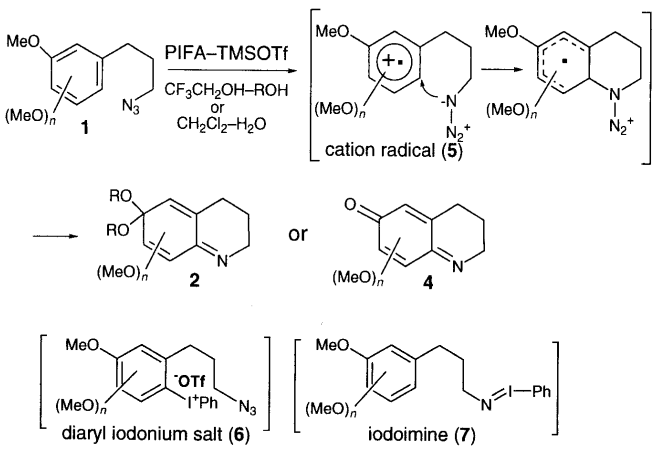

Chart 1

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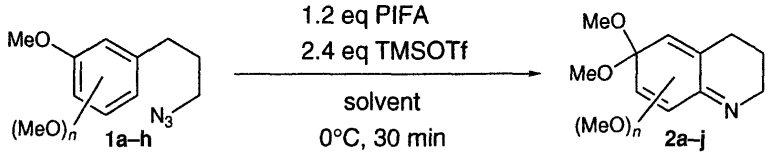
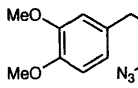
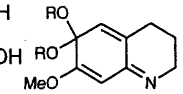
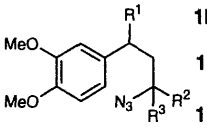
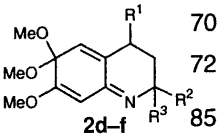
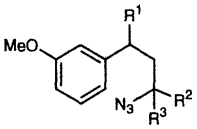
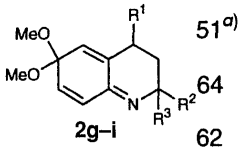
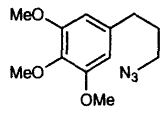
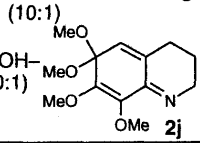
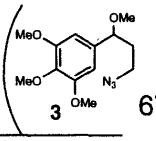
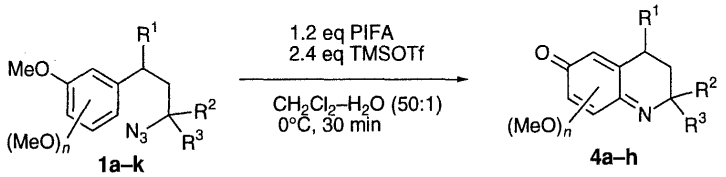
Table 1. Synthesis of Quinone Imine Ketals (**2**)

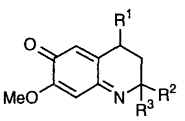
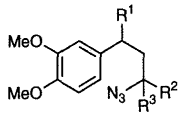
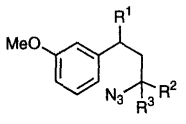
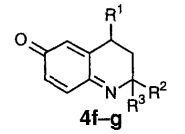
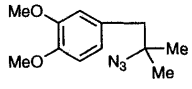
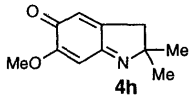


Run	Starting material	Solvent	Product	Yield (%)
1	 **1a**	CF_3CH_2OH–MeOH (10:1)	 **2a–c**	94 (R=Me)
2		$(CF_3)_2CHOH$–MeOH (10:1)		86 (R=Me)
3		CF_3CH_2OH–EtOH(10:1)		65 (R=Et)
4		CH_2Cl_2–$HO(CH_2)_2OH$(10:1)		83 (R=-CH_2CH_2-)
5	 **1b**: R^1, R^2=H, R^3=Me	CF_3CH_2OH–MeOH (10:1)	 **2d–f**	70
6	**1c**: R^1=H, R^2, R^3=Me	CF_3CH_2OH–MeOH (10:1)		72
7	**1d**: R^1=Me, R^2, R^3=H	CF_3CH_2OH–MeOH (10:1)		85
8	 **1e**: R^1, R^2, R^3=H	CF_3CH_2OH–MeOH (10:1)	 **2g–i**	51[a]
9	**1f**: R^1=H, R^2, R^3=Me	CF_3CH_2OH–MeOH (10:1)		64
10	**1g**: R^1=Me, R^2, R^3=H	CF_3CH_2OH–MeOH (10:1)		62
11	 **1h**	$(CF_3)_2CHOH$–MeOH (10:1)	 **2j** 27  **3** 67	

a) NMR yield after workup is >90%.

Table 2. Synthesis of Quinone Imines (**4**)



Run	Starting material	Product	Yield (%)
1	**1a**: R^1, R^2, R^3=H	 **4a–e**	76
2	 **1b**: R^1, R^2=H, R^3=Me		70
3	**1c**: R^1=H, R^2, R^3=Me		77
4	**1d**: R^1=Me, R^2, R^3=H		82
5	**1i**: R^1, R^2, R^3=Me		89
6	 **1f**: R^1=H, R^2, R^3=Me	 **4f–g**	57
7	**1j**: R^1, R^2, R^3=Me		75
8	 **1k**	 **4h**	45

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_3CH_2OH–MeOH or CH_2Cl_2–H_2O 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

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phenol ethers bearing an alkyl amino or an amide side-chain with PIFA–TMSOTf sometimes gave a complex mixture, probably due to competitive reactions[19] between the phenol ether moiety and the amino group.

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

Experimental

All melting points are uncorrected. NMR spectra were measured on 200, 250, 270, and 300 MHz spectrometers with $CDCl_3$ as a solvent and $SiMe_4$ 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 F_{254} for preparative thin-layer chromatography (prep. TLC) were used. Organic layers were dried with anhydrous Na_2SO_4. PIFA is commercially available.

Preparation of Phenol Ethers with an Alkyl Azido Side-chain **1a,e,h** were prepared from the corresponding methyl phenylpropionate *via* 3 steps (1) $LiAlH_4$ in tetrahydrofuran (THF), 2) I_2, PPh_3, imidazole in toluene, 3) NaN_3 in *N*,*N*-dimethylformamide (DMF)). **1b** was prepared from 3,4-dimethoxyphenyl propionicacidchloride *via* 4 steps (1) $AlMe_3$, $Cu(acac)_2$, PPh_3 in THF, 2) $NaBH_4$ in EtOH, 3) I_2, PPh_3, imidazole in toluene, 4) NaN_3 in DMF). **1c,f,i,j,k** were prepared from the corresponding methyl phenylpropionate or methyl phenylacetate *via* 2 steps (1) MeMgI in Et_2O, 2) $TMSN_3$, $BF_3 \cdot Et_2O$ in CH_2Cl_2). **1d,g** were prepared from the corresponding acetophenones *via* 5 steps (1) *n*BuLi, $(MeO)_2P(O)CH_2CO_2Me$ in THF, 2) 10%Pd–C in EtOH, 3) $LiAlH_4$ in THF, 4) I_2, PPh_3, imidazole in toluene, 5) NaN_3 in DMF).

4-(3-Azidopropyl)-1,2-dimethoxybenzene(1a) A colorless oil. IR (KBr): 2940, 2095, 1590, 1515 cm^{-1}. ^{1}H-NMR (270 MHz) δ: 1.89 (2H, tt, J=7.5, 6.6 Hz), 2.66 (2H, t, J=7.5 Hz), 3.29 (2H, t, J=6.6 Hz), 3.86 (3H, s), 3.88 (3H, s), 6.70 (1H, s), 6.72 (1H, dd, J=8.3, 2.0 Hz), 6.81 (1H, d, J=8.3 Hz). HRMS Calcd for $C_{11}H_{15}N_3O_2$: 221.1164. Found: 221.1175.

4-(3-Azidobutyl)-1,2-dimethoxybenzene(1b) A colorless oil. IR (KBr): 2935, 2100, 1590, 1520 cm^{-1}. ^{1}H-NMR (270 MHz) δ: 1.29 (3H, d, J=6.6 Hz), 1.65—1.88 (2H, m), 2.54—2.78 (2H, m), 3.37—3.50 (1H, m), 3.86 (3H, s), 3.88 (3H, s), 6.71 (1H, s), 6.72 (1H, dd, J=8.6, 2.0 Hz), 6.80 (1H, d, J=8.6 Hz). HRMS Calcd for $C_{12}H_{17}N_3O_2$: 235.1321. Found: 235.1317.

4-(3-Azido-3-methylbutyl)-1,2-dimethoxybenzene(1c) A colorless oil. IR (KBr): 2940, 2095, 1590, 1515 cm^{-1}. ^{1}H-NMR (270 MHz) δ: 1.33 (6H, s), 1.73—1.83 (2H, m), 2.58—2.68 (2H, m), 3.86 (3H, s), 3.88 (3H, s), 6.71 (1H, s), 6.72 (1H, d, J=7.6 Hz), 6.80 (1H, d, J=7.6 Hz). HRMS Calcd for $C_{13}H_{19}N_3O_2$: 249.1477. Found: 249.1473.

4-(3-Azido-1-methylpropyl)-1,2-dimethoxybenzene(1d) A colorless oil. IR (KBr): 2960, 2095, 1590, 1520 cm^{-1}. ^{1}H-NMR (270 MHz) δ: 1.27 (3H, d, J=6.9 Hz), 1.75—1.95 (2H, m), 2.74—2.89 (1H, m), 3.06—3.28 (2H, m), 3.87 (3H, s), 3.88 (3H, s), 6.70 (1H, br s), 6.71 (1H, dd, J=7.9, 2.0 Hz), 6.82 (1H, d, J=7.9 Hz). HRMS Calcd for $C_{12}H_{17}N_3O_2$: 235.1321. Found: 235.1310.

1-(3-Azidopropyl)-3-methoxybenzene(1e) A colorless oil. IR (KBr): 2940, 2100, 1600, 1585 cm^{-1}. ^{1}H-NMR (270 MHz) δ: 1.91 (2H, tt, J=7.5, 6.9 Hz), 2.69 (2H, t, J=7.5 Hz), 3.29 (2H, t, J=6.9 Hz), 3.80 (3H, s), 6.74—6.79 (3H, m), 7.22 (1H, t, J=8.0 Hz). HRMS Calcd for $C_{10}H_{13}N_3O$: 191.1058. Found: 191.1065.

1-(3-Azido-3-methylbutyl)-3-methoxybenzene(1f) A colorless oil. IR (KBr): 2970, 2095, 1605, 1585 cm^{-1}. ^{1}H-NMR (250 MHz) δ: 1.33 (6H, s), 1.74—1.83 (2H, m), 2.60—2.70 (2H, m), 3.80 (3H, s), 6.73—6.80 (3H, m), 7.21 (1H, dd, J=9.0, 8.0 Hz). HRMS Calcd for $C_{12}H_{17}N_3O$: 219.1371. Found: 219.1400.

1-(3-Azido-1-methylpropyl)-3-methoxybenzene(1g) A colorless oil. IR (KBr): 2960, 2095, 1600, 1585 cm^{-1}. ^{1}H-NMR (270 MHz) δ: 1.28 (3H, d, J=7.0 Hz), 1.80—1.89 (2H, m), 2.74—2.89 (1H, m), 3.05—3.26 (2H, m), 3.81 (3H, s), 6.73—6.80 (3H, m), 7.23 (1H, t, J=7.5 Hz). HRMS Calcd for $C_{11}H_{15}N_3O$: 205.1215. Found: 205.1226.

4-(3-Azidopropyl)-1,2,3-trimethoxybenzene(1h) A colorless oil, IR (KBr): 2940, 2095, 1590, 1510 cm^{-1}. ^{1}H-NMR (270 MHz) δ: 1.91 (2H, tt, J=7.5, 6.8 Hz), 2.66 (2H, t, J=7.5 Hz), 3.31 (2H, t, J=6.8 Hz), 3.83 (3H, s), 3.86 (6H, s), 6.40 (2H, s). HRMS Calcd for $C_{12}H_{17}N_3O_3$: 251.1327. Found: 251.1331.

4-(3-Azido-1,3-dimethylbutyl)-1,2-dimethoxybenzene(1i) A colorless oil. IR (KBr): 2930, 2095, 1590, 1520 cm^{-1}. ^{1}H-NMR (270 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, dd, J=14.3, 8.0 Hz), 2.81—2.95 (1H, m), 3.86 (3H, s), 3.89 (3H, s), 6.73 (1H, s), 6.74 (1H, dd, J=8.6, 1.7 Hz), 6.80 (1H, d, J=8.6 Hz). HRMS Calcd for $C_{14}H_{21}N_3O_2$: 263.1634. Found: 263.1660.

1-(3-Azido-1,3-dimethylbutyl)-3-methoxybenzene(1j) A colorless oil. IR (KBr): 2965, 2095, 1600, 1585 cm^{-1}. ^{1}H-NMR (250 MHz) δ: 1.15 (3H, s), 1.19 (3H, s), 1.28 (3H, d, J=6.8 Hz), 1.77 (1H, dd, J=14.3, 5.3 Hz), 1.94 (1H, dd, J=14.3, 7.8 Hz), 2.82—2.98 (1H, m), 3.80 (3H, s), 6.70—6.83 (3H, m), 7.21 (1H, t, J=7.5 Hz). HRMS Calcd for $C_{13}H_{19}N_3O$: 233.1528 Found: 233.1534.

4-(2-Azido-2-methylpropyl)-1,2-dimethoxybenzene(1k) A colorless oil. IR (KBr): 2970, 2095, 1590, 1515 cm^{-1}. ^{1}H-NMR (200 MHz) δ: 1.26 (6H, s), 2.71 (2H, s), 3.87 (3H, s), 3.88 (3H, s), 6.70—6.81 (3H, m). HRMS Calcd for $C_{12}H_{17}N_3O_2$: 235.1321. Found: 235.1322.

General Experimental Procedure Synthesis of Quinone Imine Ketals: To a stirred solution of **1** (0.100 mmol) in CF_3CH_2OH (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 $NaHCO_3$ aq. added at room temperature. The resulting mixture was extracted with CH_2Cl_2 (10 ml×3), the combined organic layer was washed with saturated $NaHCO_3$ aq., H_2O and brine, dried and evaporated *in vacuo*. The residue was purified by column chromatography or preparative TLC on silica-gel to give the corresponding quinone imine ketal **2**.

Synthesis of Quinone Imines: To a stirred solution of **1** (0.100 mmol) in CH_2Cl_2 (2 ml)–H_2O (0.04 ml) was added dropwise TMSOTf (0.24 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 $NaHCO_3$ aq. added at room temperature. The resulting mixture was extracted with CH_2Cl_2 (10 ml×3), the combined organic layer was washed with saturated $NaHCO_3$ aq., H_2O and brine, dried and evaporated *in vacuo*. The residue was purified by column chromatography on neutral alumina to give the corresponding quinone imine **4**.

Several quinone imine ketals and quinone imines decomposed during recrystallization and the measurement of the ^{13}C-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 CF_3CH_2OH (3 ml)–MeOH (0.3 ml), TMSOTf (0.061 ml, 0.314 mmol), and PIFA (67.6 mg, 0.157 mmol) gave **2a** (27.6 mg, 94%) as a colorless crystals, mp 103—108 °C (from *n*-hexane–Et_2O). IR (KBr): 2935, 1630, 1585, 1460 cm^{-1}. ^{1}H-NMR (300 MHz) δ: 1.78 (2H, tt, 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, s), 5.79 (1H, s). ^{13}C-NMR (67.5 MHz) δ: 22.8, 27.4, 50.0, 51.3, 55.5, 95.8, 104.4, 128.2, 131.1, 158.1, 159.3. *Anal.* Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.40; H, 7.56; N, 6.18.

6,6-Diethoxy-7-methoxy-2,3,4,6-tetrahydroquinoline (2b) **1a** (31.4 mg, 0.142 mmol) in CF_3CH_2OH (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–Et_2O). IR (KBr): 2940, 1670, 1625, 1585 cm^{-1}. ^{1}H-NMR (300 MHz) δ: 1.19 (6H, t, J=7.0 Hz), 1.72—1.80 (2H, m), 2.48 (2H, t, J=5.8 Hz), 3.27—3.45 (4H, m), 3.74 (3H, s), 3.77 (2H, t, J=5.5 Hz), 5.75 (2H, s). ^{13}C-NMR (75 MHz) δ: 15.4, 22.8, 27.3, 50.1, 55.3, 59.1, 95.4, 104.6, 129.7, 130.9, 158.3, 160.0. HRMS Calcd for $C_{14}H_{21}NO_3$: 251.1521. Found: 251.1505.

6,6-Ethylenedioxy-2,3,4,6-tetrahydroquinoline (2c) **1a** (26.1 mg, 0.118 mmol) in CH_2Cl_2 (2.5 ml)–$HOCH_2CH_2OH$ (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 (KBr): 2940, 1675, 1630, 1585 cm^{-1}. ^{1}H-NMR (270 MHz) δ: 1.69—1.79 (2H, m), 2.44 (2H, dt, J=6.0, 2.0 Hz), 3.72 (3H, s), 3.77 (2H, t, J=5.5 Hz), 4.07—4.18 (2H, m), 4.19—4.28 (2H, m), 5.58 (1H, s), 5.67 (1H, s). ^{13}C-NMR (67.5 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 $C_{12}H_{15}NO_3$: 221.1052. Found: 221.1066.

2-Methyl-6,6,7-trimethoxy-2,3,4,6-tetrahydroquinoline (2d) **1b** (29.5 mg, 0.125 mmol) in CF_3CH_2OH (3 ml)–MeOH (0.3 ml), TMSOTf (0.058 ml, 0.300 mmol), and PIFA (64.7 mg, 0.150 mmol) gave **2d** (20.9 mg, 70%) as a colorless oil. IR (KBr): 2940, 1675, 1630, 1580 cm^{-1}. ^{1}H-NMR (300 MHz) δ: 1.29—1.44 (1H, m), 1.35 (3H, d, J=7.0 Hz), 1.86—1.96 (1H, m), 2.39—2.61 (2H, m), 3.24 (3H, s), 3.26 (3H, s), 3.55—3.68 (1H, m), 3.75 (3H, s), 5.78 (2H, s). ^{13}C-NMR (67.5 MHz) δ: 23.2, 26.7, 30.1, 51.3, 54.6, 55.5, 95.8, 104.7, 127.8, 130.9, 157.0, 159.3. HRMS Calcd for $C_{13}H_{19}NO_3$: 237.1362. Found: 237.1362.

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2,2-Dimethyl-6,6,7-trimethoxy-2,3,4,6-tetrahydroquinoline (2e) 1c (17.4 mg, 0.070 mmol) in CF_3CH_2OH (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 colorless needles, mp 78 °C. IR (KBr): 2940, 1670, 1630, 1580 cm^{-1}. ^{1}H-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). ^{13}C-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 Calcd for $C_{14}H_{21}NO_3$: 251.1520. Found: 251.1520.

4-Methyl-6,6,7-trimethoxy-2,3,4,6-tetrahydroquinoline (2f) 1d (30.0 mg, 0.128 mmol) in CF_3CH_2OH (3 ml)–MeOH (0.3 ml), TMSOTf (0.059 ml, 0.305 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}. ^{1}H-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—2.63 (1H, m), 3.23 (3H, s), 3.25 (3H, s), 3.73 (1H, ddd, J=18.0, 8.5, 4.5 Hz), 3.75 (3H, s), 3.94 (1H, dt, J=18.0, 4.8 Hz), 5.75 (1H, s), 5.83 (1H, s). ^{13}C-NMR (67.5 MHz) δ: 19.2, 30.5, 30.8, 48.8, 51.3, 55.5, 96.1, 104.9, 126.7, 136.8, 157.7, 158.7. HRMS Calcd for $C_{13}H_{19}NO_3$: 237.1363. Found: 237.1360.

6,6-Dimethoxy-2,3,4,6-tetrahydroquinoline (2g) 1e (30.4 mg, 0.159 mmol) in CF_3CH_2OH (3 ml)–MeOH (0.3 ml), TMSOTf (0.074 ml, 0.383 mmol), and PIFA (82.0 mg, 0.191 mmol) gave **2g** (15.8 mg, 51%) as a colorless oil. IR (KBr): 2940, 1590, 1500 cm^{-1}. ^{1}H-NMR (270 MHz) δ: 1.77 (2H, tt, J=7.0, 6.0 Hz), 2.48 (2H, t, J=7.0 Hz), 3.31 (3H, s), 3.86 (2H, t, J=6.0 Hz), 5.93 (1H, br s), 6.30 (1H, dd, J=11.0, 3.0 Hz), 6.43 (1H, d, J=11.0 Hz). HRMS Calcd for $C_{11}H_{15}NO_2$: 193.1100. Found: 193.1098.

6,6-Dimethoxy-2,2-dimethyl-2,3,4,6-tetrahydroquinoline (2h) 1f (31.8 mg, 0.145 mmol) in CF_3CH_2OH (3 ml)–MeOH (0.3 ml), TMSOTf (0.067 ml, 0.347 mmol), and PIFA (74.8 mg, 0.174 mmol) gave **2h** (20.4 mg, 64%) as a colorless oil. IR (KBr): 2965, 1650, 1585 cm^{-1}. ^{1}H-NMR (200 MHz) δ: 1.26 (6H, s), 1.65 (2H, t, J=7.0 Hz), 2.50 (2H, dt, J=7.0, 2.0 Hz), 3.32 (6H, s), 5.96—5.99 (1H, m), 6.30 (1H, dd, J=10.0, 3.0 Hz), 6.42 (1H, d, J=10.0 Hz). HRMS Calcd for $C_{13}H_{19}NO_2$: 221.1416. Found: 221.1426.

6,6-Dimethoxy-4-methyl-2,3,4,6-tetrahydroquinoline (2i) 1g (32.1 mg, 0.156 mmol) in CF_3CH_2OH (3 ml)–MeOH (0.3 ml), TMSOTf (0.072 ml, 0.373 mmol), and PIFA (80.7 mg, 0.188 mmol) gave **2i** (20.0 mg, 62%) as a pale yellow oil. IR (KBr): 2960, 1590, 1500 cm^{-1}. ^{1}H-NMR (270 MHz) δ: 1.19 (3H, d, J=7.0 Hz), 1.35—1.60 (1H, m), 1.74—1.89 (1H, m), 2.42—2.63 (1H, m), 3.30 (3H, s), 3.32 (3H, s), 3.69—3.88 (1H, m), 3.94—4.09 (1H, m), 6.01 (1H, s), 6.29 (1H, d, J=11.0 Hz), 6.44 (1H, d, J=11.0 Hz). HRMS Calcd for $C_{12}H_{17}NO_2$: 207.1260. Found: 207.1262.

6,6,7,8-Tetramethoxy-2,3,4,6-tetrahydroquinoline (2j) 1h (29.7 mg, 0.118 mmol) in CF_3CH_2OH (3 ml)–MeOH (0.3 ml), TMSOTf (0.055 ml, 0.285 mmol), and PIFA (61.0 mg, 0.142 mmol) gave **2j** (8.0 mg, 27%) as a pale yellow oil. IR (KBr): 2940, 1630, 1590 cm^{-1}. ^{1}H-NMR (200 MHz) δ: 1.77 (2H, tt, J=7.0, 5.5 Hz), 2.48 (2H, dt, J=7.0, 2.0 Hz), 3.23 (3H, s), 3.77 (3H, s), 3.89 (2H, t, J=5.5 Hz), 4.05 (3H, s), 5.68 (1H, br s). HRMS Calcd for $C_{13}H_{19}NO_4$: 253.1314. Found: 253.1321.

5-(3-Azido-1-methoxypropyl)-1,2,3-trimethoxybenzene(3) 3 (22.2 mg, 67%) as a colorless oil. IR (KBr): 2940, 2100, 1730, 1595 cm^{-1}. ^{1}H-NMR (200 MHz) δ: 1.74—2.13 (2H, m), 3.25 (3H, s), 3.28—3.58 (2H, m), 3.85 (3H, s), 3.88 (6H, s), 4.12—4.25 (1H, m), 6.52 (2H, s). HRMS Calcd for $C_{13}H_{19}N_3O_4$: 281.1373. Found: 281.1366.

7-Methoxy-3,4-dihydro-6(2*H*)-quinolinone (4a) 1a (20.9 mg, 0.094 mmol) in CH_2Cl_2 (2 ml)–H_2O (0.04 ml), TMSOTf (0.044 ml, 0.228 mmol), and PIFA (48.7 mg, 0.113 mmol) gave **4a** (12.8 mg, 76%) as an unstable solid. IR (KBr): 2935, 1655, 1600 cm^{-1}. ^{1}H-NMR (200 MHz) δ: 1.78—1.93 (2H, m), 2.60—2.69 (2H, m), 3.79 (3H, s), 4.04 (2H, t, J=6.0 Hz), 6.21 (2H, br s). HRMS Calcd for $C_{10}H_{11}NO_2$: 177.0790. Found: 177.0809.

2-Methyl-7-methoxy-3,4-dihydro-6(2*H*)-quinolinone (4b) 1b (23.4 mg, 0.099 mmol) in CH_2Cl_2 (2 ml)–H_2O (0.04 ml), TMSOTf (0.046 ml, 0.238 mmol), and PIFA (51.3 mg, 0.119 mmol) gave **4b** (13.4 mg, 70%) as a pale yellow oil. IR (KBr): 2965, 1660, 1635, 1600 cm^{-1}. ^{1}H-NMR (270 MHz) δ: 1.20—1.57 (1H, m), 1.46 (3H, d, J=6.9 Hz), 1.90—2.05 (1H, m), 2.50—2.78 (2H, m), 3.68—3.90 (1H, m), 3.80 (3H, s), 6.24 (1H, s), 6.26 (1H, s). ^{13}C-NMR (67.5 MHz) δ: 23.0, 26.8, 29.8, 55.6, 56.6, 111.7, 127.0, 137.8, 154.6, 158.1, 181.9. HRMS Calcd for $C_{11}H_{13}NO_2$: 191.0946. Found: 191.0918.

2,2-Dimethyl-7-methoxy-3,4-dihydro-6(2*H*)-quinolinone (4c) 1c (19.5 mg, 0.078 mmol) in CH_2Cl_2 (2 ml)–H_2O (0.04 ml), TMSOTf (0.036 ml, 0.186 mmol), and PIFA (40.4 mg, 0.094 mmol) gave **4c** (12.3 mg, 77%) as yellow crystals, mp 122—124 °C (from Et_2O). IR (KBr): 2975, 1665, 1605 cm^{-1}. ^{1}H-NMR (300 MHz) δ: 1.34 (6H, s), 1.75 (2H, t, J=6.5 Hz), 2.67 (2H, t, J=6.5 Hz), 3.78 (3H, s), 6.22 (1H, s), 6.23 (1H, s). ^{13}C-NMR (67.5 MHz) δ: 24.1, 29.1, 33.6, 55.6, 57.0, 112.0, 127.2, 137.0, 154.4, 156.3, 181.8. HRMS Calcd for $C_{12}H_{15}NO_2$: 205.1103. Found 205.1085. *Anal.* Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.06; H, 7.16; N, 6.80.

4-Methyl-7methoxy-3,4-dihydro-6(2*H*)-quinolinone (4d) 1d (18.5 mg, 0.079 mmol) in CH_2Cl_2 (2 ml)–H_2O (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): 2925, 1655, 1630, 1595 cm^{-1}. ^{1}H-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, ddd, 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 Calcd for $C_{11}H_{13}NO_2$: 191.0946. Found: 191.0918.

7-Methoxy-2,2,4-trimethyl-3,4-dihydro-6(2*H*)-quinolinone (4e) 1i (21.2 mg, 0.086 mmol) in CH_2Cl_2 (2 ml)–H_2O (0.04 ml), TMSOTf (0.037 ml, 0.191 mmol), and PIFA (41.5 mg, 0.097 mmol) gave **4e** (15.7 mg, 89%) as yellow needles, mp 118 °C (from Et_2O). IR (KBr): 2975, 1655, 1630, 1600 cm^{-1}. ^{1}H-NMR (300 MHz) δ: 1.23 (3H, d, J=7.9 Hz), 1.24 (3H, s), 1.35 (1H, d, J=13.5 Hz), 1.42 (3H, s), 1.79 (1H, dd, J=13.5, 5.0 Hz), 2.68—2.84 (1H, m), 3.77 (3H, s), 6.22 (1H, s), 6.38 (1H, d, J=2.4 Hz). ^{13}C-NMR (75 MHz) δ: 18.3, 26.2, 27.4, 32.5, 42.6, 55.6, 57.5, 112.3, 125.4, 142.8, 154.2, 156.1, 182.5. HRMS Calcd for $C_{13}H_{17}NO_2$: 219.1259. Found: 219.1270. *Anal.* Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 70.84; H, 7.75; N, 6.33.

2,2-Dimethyl-3,4-dihydro-6(2*H*)-quinolinone (4f) 1f (24.0 mg, 0.109 mmol) in CH_2Cl_2 (2 ml)–H_2O (0.04 ml), TMSOTf (0.051 ml, 0.264 mmol), and PIFA (56.5 mg, 0.132 mmol) gave **4f** (11.0 mg, 57%) as a pale yellow solid, mp 72—76 °C. IR (KBr): 2970, 1650, 1630, 1590 cm^{-1}. ^{1}H-NMR (300 MHz) δ: 1.35 (6H, s), 1.74 (2H, t, J=7.0 Hz), 2.65 (2H, t, J=7.0 Hz), 6.23 (1H, d, J=2.0 Hz), 6.51 (1H, dd, J=10.0, 2.0 Hz), 7.04 (1H, d, J=10.0 Hz). ^{13}C-NMR (75 MHz) δ: 24.1, 28.9, 33.3, 57.7, 128.1, 131.9, 137.4, 142.2, 156.2, 187.7. HRMS Calcd for $C_{11}H_{13}NO$: 175.0997. Found 175.1013. *Anal.* Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.21; H, 7.52; N, 7.90.

2,2,4-Trimethyl-3,4-dihydro-6(2*H*)-quinolinone (4g) 1j (26.8 mg, 0.115 mmol) in CH_2Cl_2 (3 ml)–H_2O (0.06 ml), TMSOTf (0.053 ml, 0.274 mmol), and PIFA (59.3 mg, 0.138 mmol) gave **4g** (16.4 mg, 75%) as an unstable solid, mp 69—71 °C. IR (KBr): 2970, 1645, 1625, 1590 cm^{-1}. ^{1}H-NMR (270 MHz) δ: 1.24 (3H, d, J=7.7 Hz), 1.26 (3H, s), 1.35 (1H, d, J=13.5 Hz), 1.71 (3H, s), 1.81 (1H, dd, J=13.5, 4.8 Hz), 2.68—2.85 (1H, m), 6.37 (1H, s), 6.50 (1H, dd, J=10.0, 1.8 Hz), 7.05 (1H, d, J=1.8 Hz). ^{13}C-NMR (67.5 MHz) δ: 18.2, 26.4, 27.5, 32.3, 42.5, 58.0, 126.0, 131.5, 142.4, 142.9, 155.6, 187.9. HRMS Calcd for $C_{12}H_{15}NO$: 189.1154. Found: 189.1166.

2,3-Dimethyl-6-methoxy-2,3-dihydro-5*H*-indol-5-one (4h) 1k (21.1 mg, 0.090 mmol) in CH_2Cl_2 (2 ml)–H_2O (0.04 ml), TMSOTf (0.042 ml, 0.215 mmol), and PIFA (46.3 mg, 0.108 mmol) gave **4h** (7.7 mg, 45%) as an unstable solid. IR (KBr): 2965, 1665, 1600 cm^{-1}. ^{1}H-NMR (270 MHz) δ: 1.42 (6H, s), 2.73 (2H, d, J=2.0 Hz), 3.85 (3H, s), 6.41 (1H, t, J=2.0 Hz), 6.50 (1H, s). ^{13}C-NMR (67.5 MHz) δ: 29.1, 43.3, 55.8, 74.8, 103.6, 122.2, 154.6, 156.6, 162.4, 181.4. HRMS Calcd for $C_{11}H_{13}NO_2$: 191.0946. Found: 191.0932.

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