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Efficient and selective synthesis of quinoline derivatives

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ABSTRACT

The bromination reaction of 1,2,3,4-tetrahydroquinoline (**7**) was investigated by NBS and molecular bromine. One-pot synthesis is described for synthetically valuable 4,6,8-tribromoquinoline (**3**) and 6,8-dibromo-1,2,3,4-tetrahydroquinoline (**6**) on bromination of 1,2,3,4-tetrahydroquinoline (**7**) in efficient yields (75 and 90%, respectively). 6-Bromo- (**4**) and 6,8-dibromo-1,2,3,4-tetrahydroquinolines (**6**) were converted to 6-bromo- (**1**) and 6,8-dibromo quinolines (**2**), respectively, by aromatization with DDQ in 83 and 77% yields, respectively. Several novel trisubstituted quinoline derivatives were efficiently prepared via lithium–halogen exchange reactions of tribromide **3**. Treatment of 4,6,8-tribromoquinoline with BuLi followed by quenching with electrophiles [$Si(CH_3)_3Cl$, $S_2(CH_3)_2$, I_2] regioselectively proceeded at C-4 and C-8 sites and afforded corresponding 4,8-disubstituted-6-bromoquinolines. Similarly, lithiation of tribromide **3** followed by addition of water to the intermediate produced 6-bromoquinoline in 65% yield. Copper-induced nucleophilic substitution of tribromide **3** with NaOMe afforded 4,6,8-trimethoxyquinoline (**17**) in 60% yield.

1. Introduction

The presence of the quinoline skeleton in the frameworks of pharmacologically active compounds and natural products has spurred on the development of different strategies for their synthesis. Quinoline derivatives have long been known for their wide range of biological activities[1] and chemotherapeutic activities.[2] In addition, they are used as dyestuffs and photographic sensitizers.[3] They are valuable reagents for the synthesis of nano- and mesostructures with enhanced electronic and photonic properties.[4]

Bromoquinolines have been of interest for chemists as precursors for heterocyclic compounds with multifunctionality, giving accessibility to a wide variety of compounds through, e.g., couplings and Grignard reactions. These building blocks have especially been used within medicinal chemistry as starting materials for numerous compounds with pharmacological activity.

Ring substitution of quinoline by halogens is rather complex, with products depending on the conditions used. Earlier works indicate that direct bromination of quinoline is difficult because quinoline is electron-deficient in nature and because of the easy formation of *N*-bromo complexes.[5] The conflicting results obtained previously may have been due to inadequate separation and identification methods.

3-Bromoquinoline is conveniently prepared in 82% yield by heating the quinoline–bromine adduct in an inert solvent with pyridine as the hydrogen bromide scavenger.[5] The treatment of quinoline in concentrated sulfuric acid containing silver sulfate with one mole of bromine results in a mixture of 5- and 8-bromoquinoline in about equal quantities and some 5,8-dibromoquinoline.[6] 5-Bromoquinoline is formed in 78% yield if the quinoline–aluminum chloride complex is heated with bromine.[7] Further bromination in sulfuric acid or in the presence of aluminum chloride yields 5,8-dibromo-, 5,6,8-tribromo-, and 5,7,8-tribromoquinolines.[7]

Several different strategies for the preparation of substituted quinolines are known. Most synthetic routes leading to these cyclic structures consist of cyclization reactions starting from benzene (or cyclohexane) derivatives substituted with nitrogen functions.[8] Such reactions include the Skraup, Friedlander, Doebner-von Millet, and Combes syntheses.[9] Although different methods are described in the literature for the synthesis of the quinoline ring, these methods allow restricted synthesis of quinoline derivatives, especially in the case of di- and trisubstituted derivatives.

Recently we developed simple and selective bromination methods on naphthalene, hydronaphthalenes, and anthracene.[10] As an extension of these works we are interested in the bromination of azanaphthalenes, i.e., quinoline and isoquinoline. In this report, one-pot synthesis of 4,6,8-tribromoquinoline (**3**) by direct

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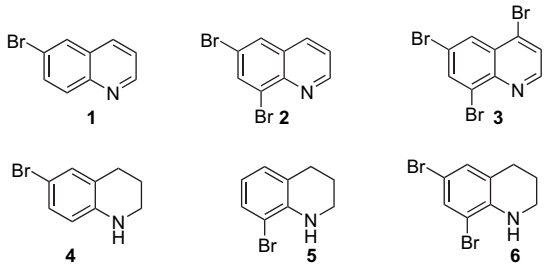
bromination of 1,2,3,4-tetrahydroquinoline (THQ, **7**) is presented and the values of brominated products **3** as precursors to the corresponding substituted quinoline derivatives are illustrated. We describe selective and convenient synthesis methods for 6-bromo- (6-BrQ, **1**), 6,8-dibromoquinoline (6,8-diBrQ, **2**), 6-bromo-(6-BrTHQ, **4**), and 4,6-dibromo-1,2,3,4-tetrahydroquinoline (6,8-diBrTHQ, **6**) (Scheme 1).



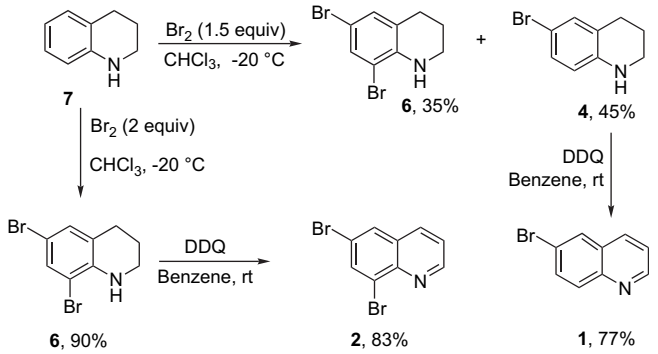
Scheme 1.

2. Results and discussion

The reaction of THQ **7** with 1 equiv of NBS was examined in CCl_4 under reflux. After the reaction, ^{1}H NMR spectra of the mixture products indicated 6-BrTHQ **4**, 8-BrTHQ **5**, 6,8-diBrTHQ **6**, 4,6,8-TriBrQ **3**, and the starting material (THQ, **7**) in a ratio of 31:8:36:5:20. After silica gel chromatography combined with preparative TLC, the compounds were isolated in yields of 22% for **4**, 8% for **5**, 16% for **6**, and 2% for **3**.

We studied the same reaction under photolytic conditions. For irradiation, a projector lamp (250 W, visible light) in an immersion photochemical apparatus was used. A new product 6,8-diBrQ **2** appeared and the product ratio was changed. Photobromination of THQ **7** with 2 and 3 equiv of NBS also resulted in the formation of a complex mixture. With molecular bromine, the bromination of THQ **7** is more selective and effective. Bromination of THQ with 1 equiv of bromine afforded a mixture of 6-BrTHQ **4** and 6,8-diBrTHQ **6** (product ratio: 25:50 for **4** and **6**, conv. 75%) at room temperature. However, the product ratio changed at lower temperature and the conversion increased. When the bromination was repeated at −23 °C using 1.5 equiv of Br_2, 6-BrQ **4** and 6,8-diBTHQ **6** were obtained in 50:50 ratio as assigned by NMR spectra. The product mixture was efficiently and easily separated by short silica gel column chromatography eluting with hexane–ethylacetate (Scheme 2). On the other hand, 6,8-diBrTHQ **6** was obtained as the sole product in efficient yield (90%) upon treatment of THQ with 2 equiv of bromine (Scheme 2).

^{1}H NMR spectra of 6-BrTHQ **4** consist of aryl Hs, alkyl Hs, and NH signals (Table 1). Resonance of H_5 is a singlet at δ 7.10, which is clear



Scheme 2.

Table 1
^{1}H NMR data of compounds **4**–**6**

Compounds	Proton								Coupling constants (Hz)
	1	2	3	4	5	6	7	8	
4	3.80 s	3.40 t	1.91 p	2.71 t	7.10 s	—	6.32 d	7.05 d	J_{78}=8.3 J_{32}=5.8
5	3.60 s	3.40 t	1.92 p	2.75 d	7.17 d	6.40 t	6.96 d	—	J_{56}=7.8 J_{67}=7.8 J_{32}=5.8 J_{43}=6.3
6	4.43 s	3.34 t	1.92 p	2.73 t	7.31 d	—	6.96 d	—	J_{57}=1.6 J_{32}=5.8 J_{43}=6.3

evidence for the 6-bromo structure. H_7 and H_8 resonate as an AB system (δ 6.32 and 7.05, J_{78}=8.3 Hz). Nine ^{13}C NMR resonance signals of the compound are accord with the suggested structure. ^{1}H NMR spectra of 6,8-diBrTHQ clearly show a 6,8-dibromo structure due to two aryl signals with a meta coupling constant (Table 1). Three aliphatic and NH shifts [δ 3.34 (t), 2.73 (t), 1.92 (p), 4.43 (br s, NH)] are in accord with the expected product. In the ^{13}C NMR spectra, the four quaternary carbon resonances in the sp^2 region are also in agreement with the suggested structure.

Obviously, 6,8-diBrTHQ **6** and 6-BrTHQ **4** are precursors for 6,8-diBrQ **2** and 6-BrQ **1**, respectively. Therefore, they were submitted to aromatization with DDQ. After reactions, 6,8-diBrQ and 6-BrQ were obtained in high yields (83 and 77%, respectively). In the ^{1}H NMR spectra of 6,8-diBrQ, shifting downfield resonance of H_2 (9.04 ppm, dd) is characteristic for quinoline rings. The doublet of doublets (J_{23}=4.2 Hz, J_{34}=8.3 Hz) of H_3 and H_4 appears at δ 7.49 and 8.09. Two signals with meta coupling are also in good agreement with the structure (δ 8.16 and 7.96, J_{57}=2.4 Hz). The ^{13}C NMR spectra of dibromide consist of nine sp^2 resonances, four of which are quaternary carbons. In the NMR spectra of 6-BrQ **1**, two AB systems (H_3 and H_4) and (H_7 and H_8) are consistent with the suggested structure. A singlet of H_5 appears at δ 8.00 and a doublet of H_2 at δ 8.90 (J_{23}=2.6 Hz) (Table 2). The ^{13}C NMR spectra are consistent with a monobromoquinoline structure. 6-BrQ **1** is prepared

Table 2
^{1}H NMR data of compounds **1**–**3** and **13**–**17**

Compounds	Proton						Coupling constants (Hz)/other signals
	2	3	4	5	7	8	
1	8.90 d	7.44 dd	8.10 d	7.90 s	7.80 dd	8.00 d	J_{34}=8.3 J_{23}=2.6 J_{78}=9.2 J_{57}=2.2
2	9.04 dd	7.49 dd	8.09 dd	7.96 d	8.16 d	—	J_{23}=4.2 J_{24}=1.6 J_{57}=2.4 J_{34}=8.3
3	8.99 d	8.20 d	—	8.14 d	7.86 d	—	J_{57}=2.2 J_{23}=2.2
13	8.99 d	8.14 d	—	7.96 d	7.86 d	—	J_{23}=1.5, J_{57}=2.1 *Silyl* δ 0.39 s, 0.45 s
14	8.76 d	8.20 d	—	7.60 d	7.79 d	—	J_{23}=3.0, J_{57}=2.0 *SCH_3* δ 3.07, 3.05
15	9.05 d	8.40 d	—	8.35 d	7.80 d	—	J_{57}=2.7 J_{23}=2.0
16	9.00 dd	7.42 dd	8.00 dd	7.95d	8.40 d	—	J_{57}=2.6 J_{23}=4.2 J_{34}=8.3 J_{24}=1.6
17	8.40 d	7.18 d	—	6.40 d	6.50 d	—	J_{23}=2.7, J_{57}=2.4 *OMe* δ 3.87 s, 3.89 s, 3.97 s

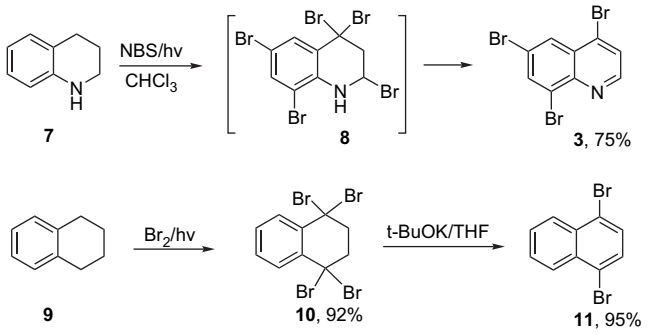
by the Skraup synthesis starting from the *p*-bromoaniline.[5,11] Incorporation of 6-BrQ **1** into novel chelating ligands is important for the construction of useful molecular devices in field of nanoscale chemistry.[12]

Finally, photobromination of THQ **7** with 5 equiv of NBS in CCl_4 at reflux temperature of the solvent was carried out. For irradiation, a projector lamp (70 W, visible light) in an immersion photochemical apparatus was used. Interestingly, the reaction produced 4,6,8-tribromoquinoline (**3**) in the absence of other products. After the reaction, tribromide **3** was obtained as a sole product in a yield of 50%. When the NBS bromination was carried out at room temperature in $CHCl_3$, surprisingly, the yield increased to 75% and the reaction period was shorter.

The structure of **3** was determined by ^1H and ^{13}C NMR spectroscopy, including 2D NMR experiments (COSY, HETCOR) and high resolution mass spectrometry. The formula of compound **3** ($C_9H_4NBr_3$) was determined by HR-ESIMS (362.790454, calculated by mass spectrometry 362.789382). The ^1H NMR spectrum of tribromide **3** consists of four signals (Table 1). H_2 appears at δ 8.99 with a lower coupling constant value (J_{23}=2.2 Hz), which is characteristic for a quinoline ring. Meta coupling doublet of H_7 and H_5 is clear evidence for the position of bromines. The ^{13}C NMR studies of compound **3** displayed nine resonances; five signals of these are quaternary in accord with the molecule skeleton being bonded to three bromine atoms.

We assume that the one-pot reaction giving tribromide **3** actually consists of five sequential reaction steps. Aniline-like resonances of tetrahydroquinoline led to substitution at the C-6 and C-8 sites of the aryl ring. We also assume that the reaction probably proceeds through the pentabromide **8** and subsequent aromatization results in the formation of tribromide **3**.

We revealed that double bromination occurs at benzylic sites of tetraline (**9**) (Scheme 3).[10f] Therefore, we assume that THQ **7** reacts at C-4 and C-3 positions of higher reactivity (Scheme 3).



Scheme 3.

The lithium–halogen exchange reaction is the method of choice for the preparation of new heteroaromatic compounds.[13] Therefore, to demonstrate its value as a precursor for other useful compounds, tribromoquinoline **3** was investigated by metal–halogen exchange using BuLi, followed by the addition of electrophiles for the preparation of new derivatives.

Treatment of tribromide with 2 equiv of BuLi and subsequent addition of water resulted in 6-bromoquinoline (**1**) as the sole product in a yield of 65%. To determine if this reaction was general for other electrophiles, a study was carried out and the results are shown in Scheme 4. After lithiation, treatment of dilithioquinoline (**12**) with trimethylsilyl chloride gave 6-bromo-4,8-trimethylsilylquinoline (**13**), while treatment with 1,2-dimethyldisulfane afforded 6-bromo-4,8-bis(methylthio) quinoline (**14**) in high yields (90%) and as sole product.

The two silyl signals in compound **13** and two dimethylthio signals in compound **14** in the NMR spectra are clear evidence of the formation of the compounds. Treatment of dilithio (**6**) with iodine gave two iodo derivatives (**15** and **16**) after chromatography. The similarity of the signal systems of compounds **3** and **15** (the same is true for compounds **2** and **16**) is quite helpful for identification of the structures of iodines **15** and **16**.

Lastly, tribromide **3** was treated with MeONa in the presence of CuI in DMF at ca. 100 °C according to the literature method (Scheme 4).[14] Copper-induced substitution of tribromide **3** resulted in the formation of 4,6,8-trimethoxyquinoline (**17**) as the sole product (ca. 60%). Trimethoxide **17** exhibits a similar ^1H NMR spectrum to that of the tribromide **3**, with the lower shifting due to donor methoxy protons (Table 1).

3. Conclusion

We demonstrated that 1,2,3,4-tetrahydroquinoline (**7**) is quite reactive toward bromination. Therefore, the difficulty in the bromination of quinoline due to the formation of *N*-bromo complexes or its electron-deficient nature is not a problem in case of THQ **7**. We opened up a new route to quinoline derivatives using commercially available and cheap starting material THQ 7, which is obtained by the simple reduction of quinoline. Convenient and selective reaction procedures are described for 6-BrQ **1**, 6,8-diBrQ **2**, 4,6,8-triBrQ **3**, 6-BrTHQ **4**, and 6,8-diBrTHQ **6**, which can be converted to corresponding substituted quinolines and tetrahydroquinolines, which are otherwise difficult to obtain. In summary, the lithium–halogen exchange reaction of 4,6,8-triBrQ **3** provides a method for synthesizing 4,8-disubstituted-6-bromoquinolines. The lithium–halogen exchange reaction of 4,6,8-triBrQ **3**, 6,8-diBrQ **2**, 6-BrTHQ **4**, and 6,8-diBrTHQ **6** may serve for the synthesis of natural bioactive quinolines derivatives because there are many biological active quinolines functionalized 4,6, or 8- positions such as quinine, pentaquine, and plasmoquine.

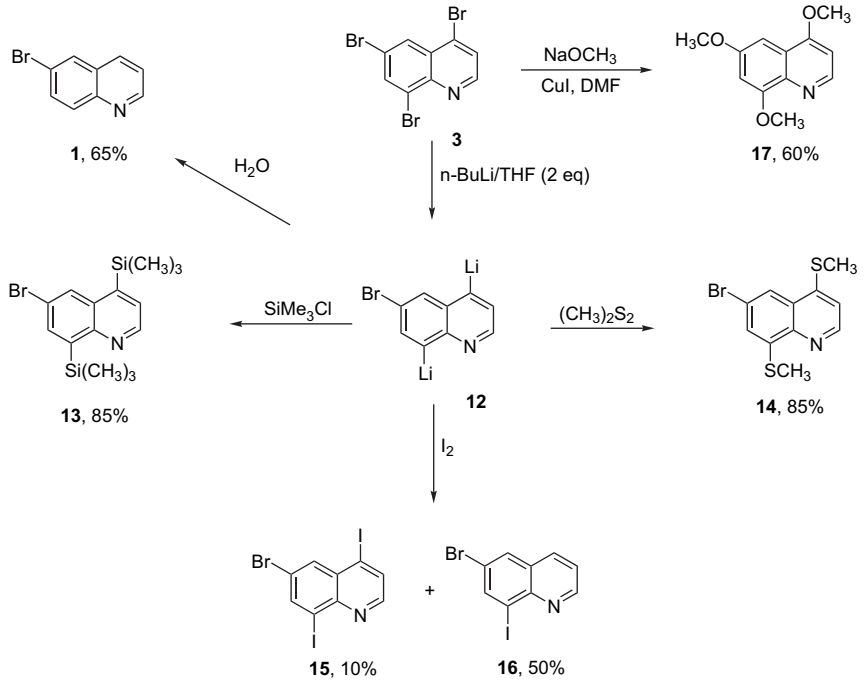
4. Experimental

4.1. General

Thin layer chromatography was carried out on Merck silica F_{254} 0.255 mm plates and spots were visualized by UV fluorescence at 254 nm. Classic column chromatography was performed using Merck 60 (70–230 mesh) silica gel. Melting points were determined on a Thomas-Hoover capillary melting points apparatus. Solvents were concentrated at reduced pressure. IR spectra were recorded on a Perkin–Elmer 980 instrument. Mass spectra were recorded on a VG Zab Spec GC–MS spectrometer under electron-impact (EI) and chemical ionization conditions. NMR spectra were recorded on Bruker 400 MHz for ^1H and at 100 MHz for ^{13}C NMR.

4.2. Bromination of 1,2,3,4-tetrahydroquinoline (7) with 1 equiv of NBS

To a solution of 1,2,3,4-tetrahydroquinoline (1.0 g, 7.5 mmol) in CCl_4 (20 mL) were added AIBN (18 mg, 0.10 mmol) as catalyst and NBS (1.33 g, 7.5 mmol). Drying tube containing pellet KOH for absorbing the evolved hydrogen bromide was attached to the condenser. The magnetically stirred mixture was irradiated for 5 h under reflux (77 °C). Reaction progress was monitored with TLC. After the reaction was complete, the precipitated succinimide particles were removed by filtration and washed with CCl_4 at 0 °C. The solvent was removed by vacuum and the residue was redissolved in $CHCl_3$ (30 mL). After removing the solvent, the residue (1.18 g) was subjected to silica gel (85 g) column chromatography combined with preparative thin layer chromatography eluting with



Scheme 4.

EtOAc/hexane (1:20). 8-BrTHQ **5** (110 mg, 7%), 6-BrTHQ **4** (240 mg, 15%), 6,8-diBrTHQ **6** (240 mg, 11%), and 4,6,8-triBrTHQ **3** (50 mg, 2%) were isolated. R_f values (EtAcO–hexane, 1:9) for compounds **4**, **5**, **7**, **6**, and **3** are 0.33, 0.34, 0.40, 0.60, and 0.70, respectively. Because pure 8-BrTHQ **5** could not be obtained due to the very similar R_f values of the compounds, the ^{13}C NMR and IR spectrometer values of **5** are not available.

*4.2.1. 6-BrTHQ **4***

Pale yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.10 (s, 1H, H_5), 7.05 (d, J_{87}=8.6 Hz, 1H, H_8), 6.32 (d, J_{78}=8.3 Hz, 1H, H_7), 3.40 (t, J_{23}=5.8 Hz, 2H, H_2), 2.71 (t, J_{43}=6.3 Hz, 2H, H_4), 1.91 (p, J_{32}=5.8 Hz, 2H, H_3), 3.8 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.0, 132.1, 129.8, 123.6, 115.8, 108.4, 42.2, 27.1, 21.9; IR (neat, cm^{-1}) ν_{max} 3450, 3047, 1589, 1540, 1457, 1305, 1083, 968, 904, 871, 856, 815, 781, 680, 595. Anal. Calcd for $C_9H_{10}NBr$ (212.09): C, 50.97; H, 4.75. Found: C, 51.07; H, 4.80.

*4.2.2. 8-BrTHQ **5***

Pale yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.17 (d, J_{56}=7.8 Hz, 1H, H_5), 6.96 (d, J_{76}=7.8 Hz, 1H, H_7), 6.40 (t, J_{65}=J_{67}=7.8 Hz, 1H, H_6), 3.40 (t, J_{23}=5.8 Hz, 2H, H_2), 2.75 (t, J_{43}=6.3 Hz, 2H, H_4), 1.92 (p, J_{32}=5.8 Hz, 2H, H_3), 3.60 (s, 1H, NH).

*4.2.3. 6,8-DiBrTHQ **6***

Pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J_{57}=1.6 Hz, 1H, H_5), 6.96 (d, J_{75}=1.6 Hz, 1H, H_7), 3.34 (t, J_{23}=5.8 Hz, 2H, H_2), 2.73 (t, J_{43}=6.3 Hz, 2H, H_4), 1.92 (p, J_{32}=5.8 Hz, 2H, H_3), 4.43 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 141.0, 132.0, 131.1, 124.4, 108.8, 107.2, 42.1, 27.5, 21.5; IR (neat, cm^{-1}) ν_{max} 3416, 2927, 2837, 1592, 1497, 1466, 1291, 1164, 856, 616. Anal. Calcd for $C_9H_9NBr_2$ (290.98): C, 37.15; H, 3.12. Found: C, 37.20; H, 3.16.

4.3. Photobromination of 1,2,3,4-tetrahydroquinoline with 1 equiv of NBS

To a solution of 1,2,3,4-tetrahydroquinoline (**7**) (1.0 g, 7.5 mmol) in CCl_4 (20 mL) in an internal type photochemical reaction apparatus (cylindrical immersion-well reaction apparatus, 80 mL) were added AIBN (18 mg, 0.10 mmol) and NBS (1.34 g, 7.5 mmol). Drying tube containing pellet KOH for absorbing the evolved hydrogen bromide was attached to the side arms of the apparatus. Stirring was performed with simultaneous irradiation with a projector lamp (70 W projector lamp) under reflux. Upon completion of the reaction (1 h), the resulting succinimide was collected on a filter and the filtrate concentrated under vacuum. The crude product was dissolved in chloroform (30 mL), washed with water (7×20 mL), and dried over sodium sulfate. The solvent was removed in vacuo. The mixture consisted of 6,8-diBrTHQ **6**, 6-BrTHQ **4**, 4,6,8-TriBrQ **3**, and 6,8-diBrQ **2** in a ratio of 55:30:10:5 as assigned by ^1H NMR.

4.4. Synthesis of 4,6,8-tribromoquinoline (3)

Method A. A solution of 1,2,3,4-tetrahydroquinoline (1.0 g, 7.5 mmol) in CCl_4 (20 mL) in an internal type photochemical reaction apparatus (cylindrical immersion-well reaction apparatus, 80 mL) were added NBS (1.1 equiv, 1.52 g, 8.5 mmol) and AIBN (18 mg, 0.10 mmol) as catalyst. The drying tube containing pellet KOH for absorbing the evolved hydrogen bromide was attached to the side arms of the apparatus. The magnetically stirred mixture was irradiated with a sun lamp (70 W projector lamp, cooled by air pump). First, 1 equiv of NBS (1.52 g, 8.5 mmol, 1.1 equiv) was added to the solution. In total 5.5 equiv of NBS (7.6 g, 42.5 mmol) was added over 6 h, adding 1 equiv per hour. The reaction mixture was irradiated for 6 h under reflux. Turbidity was observed due to the precipitated material (i.e., succinimide). Upon completion of the reaction (TLC monitoring), the resulting reaction mixture was cooled (0 °C) and the succinimide formed was collected on a filter and the solvent (CCl_4) was removed from the filtrate under vacuum. The precipitated residue was dissolved in chloroform (30 mL) and washed with water (7×20 mL). The organic layer was dried over Na_2SO_4. After removing the solvent and recrystallizing from CH_2Cl_2–hexane (2:1, 15 mL) in a refrigerator, 4,6,8-tribromoquinoline (**3**) was obtained (1.34 g, 50%) as white solid cubic crystals, mp 168–170 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 8.99 (d, J_{23}=2.2 Hz, 1H, H_2),

8.14 (d, J_{57}=2.2 Hz, H_5), 7.86 (d, J_{75}=2.2 Hz, 1H, H_7), 8.20 (d, J_{32}=2.2 Hz, 1H, H_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.7, 142.7, 136.7, 136.6, 131.0, 128.9, 126.0, 121.6, 119.7; MS (EI) *m*/*z* 365, 363, 286, 205, 126; HRMS (EI) calcd for $C_9H_4NBr_3$ (M^+): 362.7893, found: 362.7904; IR (KBr, cm^{-1}) ν_{max} 3160, 2545, 2329, 1693, 1373, 1294, 1193, 1002, 935, 819, 640, 555, 424.

Method B. To a solution of 1,2,3,4-tetrahydroquinoline (**7**) (1.0 g, 7.5 mmol) in $CHCl_3$ (80 mL) in an internal type photochemical reaction apparatus (cylindrical immersion-well reaction apparatus) were added NBS (6.8 g, 8.5 mmol) and AIBN (120 mg, 0.10 mmol) as catalyst. The magnetically stirred mixture was irradiated with a sun lamp (70 W projector lamp). No turbidity was observed and precipitated material (i.e., succinime particles) was collected in the bottom of the flask. Upon completion of the reaction (TLC monitoring), the resulting reaction mixture was cooled (0 °C) and the succinimide particles formed were collected on a filter and the filtrate was washed with water (30 mL×7). After removing the solvent the residue was filtered through silica gel (10 g, eluted with hexane–EtOAc) and recrystallized from CH_2Cl_2–hexane (5:1, 30 mL) and 4,6,8-tribromoquinoline (**3**) was obtained in 75% yield (2.7 g).

4.5. Bromination of THQ 7 with molecular bromine

To a solution of 1,2,3,4-tetrahydroquinoline (**7**) (0.5 g, 3.75 mmol) in $CHCl_3$ (15 mL) was added a solution of bromine (0.66 g, 4.13 mmol) in $CHCl_3$ (5 mL) over 5 min. The mixture was stirred at room temperature for 2 h in the dark. After completion of the reaction (bromine consumed completely), the resulting yellow solid was dissolved in $CHCl_3$ (15 mL). The organic layer was washed with 5% $NaHCO_3$ solution (3×15 mL) and dried over Na_2SO_4. After evaporation of the solvent, NMR analysis of the residue (0.96 g) showed the formation of 6,8-diBrTHQ **6** and 6-BrTHQ **4**. The reaction conversion was 75%. When the reaction was repeated at −78 °C under the same reaction conditions, the conversion was 90% and the product ratio was 20:70 for 6,8-diBrTHQ **6** and 6-BrTHQ **4**, respectively, as assigned by ^{1}H NMR.

Bromination of THQ **7** was repeated with 1.5 equiv of bromine at −20 °C in the dark. The starting material (THQ, 0.27 g, 2.02 mmol) in $CHCl_3$ (20 mL) was combined with solution of bromine (0.486 g, 3.04 mmol) in $CHCl_3$ (5 mL). After completion of the reaction (25 min), the resulting yellow solid was dissolved in $CHCl_3$ (20 mL). The organic layer was washed with $NaHCO_3$ solution (5%, 3×20 mL) and dried over Na_2SO_4. Mixture of 6,8-diBrTHQ **6** and 6-BrTHQ **4** was formed in ratio of 1:1 as assigned by ^{1}H NMR. The product mixture (450 mg) was applied to a short silica gel (20 g) chromatography column eluting with hexane–EtOAc (600 mL, 4:2) (R_f=0.5 for **6** and 0.25 for **4**). 6,8-DiBrTHQ **6** was collected as first eluant (350 mL). Solvent polarity was increased to 9:4 (hexane–EA) ratio. 6,8-DiTHQ **6** (206 mg, 35%) and 6-BrTHQ **4** (193 mg, 45%) were isolated in pure forms.

4.6. Synthesis of 6,8-dibromo-1,2,3,4-tetrahydroquinoline (6)

To a solution of 1,2,3,4-tetrahydroquinoline (1 g, 7.5 mmol) in $CHCl_3$ (20 mL) was dropped bromine (2.56 g, 16 mmol) in $CHCl_3$ (10 mL) over 5 min in the dark and at −20 °C. After completion of the reaction (bromine consumed completely, 2 h), the solid was dissolved in $CHCl_3$ (25 mL) and the organic layer was washed with 5% $NaHCO_3$ solution (3×20 mL) and dried over Na_2SO_4. After evaporation of the solvent, the crude material (2.12 g) was passed through a short alumina column eluting with EtOAc–hexane (1:19, 250 mL) (hexane–EA, 9:1, R_f=0.6). The pale yellow oil residue at room temperature was solidified in a freezer (−20 °C). The mixture was recrystallized from the solvent (CH_2Cl_2–petroleum ether) in a freezer (−20 °C) to give pure 6,8-dibromo-1,2,3,4-tetrahydroquinoline (**6**) in 90% yield (1.97 g).

4.7. Synthesis of 6,8-dibromoquinoline (2)

DDQ (2 g, 6.35 mmol) was dissolved in freshly distilled and dried benzene (30 mL) under an argon atmosphere. To a solution of 6,8-diBrTHQ **6** (0.88 g, 3.02 mmol) in benzene (30 mL) was added the solution of DDQ. The mixture was refluxed at 80 °C for 44 h. Upon cooling, the dark green solidified mixture was filtered and the solvent was removed in vacuo. The residue was filtered from a short silica column (1:9, EtOAc–hexane, R_f=0.65). Recrystallization of the product from hexane–chloroform gave 6,8-diBrQ **2** in a yield of 83% (725 mg), white needle crystals, mp 99–100 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.04 (dd, J_{23}=4.2 Hz, J_{24}=1.6 Hz, 1H, H_2), 8.16 (d, J_{57}=2.4 Hz, 1H, H_7), 8.09 (dd, J_{43}=8.3 Hz, J_{24}=1.6 Hz, 1H, H_4), 7.96 (d, J_{57}=2.4 Hz, 1H, H_5), 7.49 (dd, J_{32}=4.2 Hz, J_{34}=8.3 Hz, 1H, H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.5, 144.1 135.9, 135.7, 130.1, 129.7, 125.9, 122.7, 119.9; IR (KBr, cm^{-1}) ν_{max} 3414, 3069, 3028, 2924, 1955, 1923, 1638, 1617, 1588, 1547, 1481, 1469, 1348, 1308, 1290, 1084, 964, 861, 780, 676, 594. Anal. Calcd for $C_9H_5NBr_2$ (286.95): C, 37.67; H, 1.76. Found: C, 37.78; H, 1.82.

4.8. Synthesis of 6-bromoquinoline (1)

DDQ (504 mg, 1.68 mmol) was dissolved in dry benzene (20 mL) under argon atmosphere. To a solution of 6,8-diBrTHQ **6** (180 mg, 0.84 mmol) in dry benzene (20 mL) was added the solution of DDQ. The mixture was refluxed at 80 °C for two days. The dark green solidified mixture was filtered and the solvent was removed in vacuo. The residue was filtered from a short silica column (1:9, EtOAc–hexane). Recrystallization of the product from hexane–chloroform gave 6-diBrQ **1** in a yield of 77% (145 mg), brownish oil. ^{1}H NMR (400 MHz) δ 8.90 (d, J_{23}=2.6 Hz, 1H, H_2), 8.10 (d, J_{34}=8.3 Hz, 1H, H_4), 8.00 (d, J_{87}=9.2 Hz, 1H, H_8), 7.90 (d, J_{57}=2.2 Hz, 1H, H_5), 7.80 (dd, J_{78}=9.2 Hz, J_{75}=2.2 Hz, 1H, H_7); ^{13}C NMR (100 MHz) δ 150.7, 146.8, 135.1, 133.0, 131.2, 129.8, 129.5, 121.9, 120.5; IR (KBr, cm^{-1}) ν_{max} 3450, 1635, 1589, 1540, 1457, 1305, 1083, 968, 904, 871, 856, 815, 781, 680, 595, 526 cm^{-1}. CAS Number: 005332-25-2.

*4.8.1. 6-Bromoquinoline (**1**)*

n-Butyllithium (4 mL, 1.6 M, 6.03 mmol, 2.2 equiv) was added to a vacuum-dried flask containing tribromide **3** (1 g, 2.74 mmol) in THF (20 mL) at −78 °C. After the mixture was stirred for 90 min, distilled water (3.0 mL) was added at −78 °C. The mixture was stirred at −78 °C for 30 min and then at room temperature for 1 h. After quenching the mixture with water (30 mL), the aqueous layer was extracted with diethyl ether (3×20 mL), and the combined organic layers were sequentially washed with water (2×20 mL) and dried over sodium sulfate. After removing the solvent with evaporation the crude product was purified by short column chromatography (9:1, hexane-EtOAc, R_f=0.92), and after recrystallization from EtOAc–hexane (2:1) 6-bromoquinoline (**1**) was obtained in a yield of 65% (370 mg).

Note. When the lithiation of tribromide **3** and subsequent water addition reaction was carried out using 1 equiv of *n*-BuLi instead of 2 equiv of *n*-BuLi, a complex reaction mixture was obtained. ^{1}H NMR analysis of the mixture revealed 4,6-dibromoquinoline as the main product along with 6-BrQ **1**, 6,8-diBrQ **2**, and small amounts of some other unidentified products. The attempts to separate the mixture did not lead to any pure compounds.

4.9. 6-Bromo-4,8-bismethlysilylquinoline (13)

n-Butyllithium (4 mL, 1.6 M, 6.03 mmol, 2.2 equiv) was added to a vacuum-dried flask containing tribromide **3** (1 g, 2.74 mmol) in THF (20 mL) at −78 °C. After the mixture was stirred for 90 min, chlorotrimethylsilane (4.0 mL, 3.42 mmol) was added at −78 °C.

The mixture was stirred at −78 °C for 30 min and then at room temperature for 1 h. After quenching the mixture with water (30 mL), the aqueous layer was extracted with diethyl ether (3×25 mL), and the combined organic layers were washed sequentially with water (2×25 mL) and dried over sodium sulfate. The solvent was removed by rotary evaporation and the crude product was purified by short silica gel column chromatography (CH_2Cl_2–hexane, 1:4, R_f=0.90) to give **13** (860 mg, 90%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (d, J_{23}=1.5 Hz, 1H, H_1,), 8.14 (d, J_{32}=1.5 Hz, 1H, H_3), 7.96 (d, J_{57}=2.1 Hz, 1H, H_5,), 7.86 (d, J_{75}=2.1 Hz, 1H, H_7), 0.45 (s, 3H), 0.39 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 154.0, 152.2, 146.0, 142.4, 140.0, 134.4, 132.0, 129.6, 121.7, 0.9, 0.0; IR (neat, cm^{-1}) ν_{max} 2935, 1571, 1461, 1405, 1361, 1249, 1218, 1101, 993, 925, 840, 809, 754, 694, 644. Anal. Calcd for $C_{15}H_{22}BrNSi_2$ (352.42): C, 51.12; H, 6.29. Found: C, 51.17; H, 6.33.

4.10. 6-Bromo-4,8-bis(methylthio)quinoline (14)

n-Butyllithium (4 mL, 1.6 M, 6.03 mmol, 2.2 equiv) was added to a vacuum-dried flask containing tribromide **3** (1 g, 2.74 mmol) in THF (20 mL) at −78 °C. After stirring for 90 min, 1,2-dimethyldisulfane [$(CH_3S)_2$, 1.6 mL, 6.85 mmol] was added to the mixture at −78 °C. The mixture was stirred at −78 °C for 30 min and then at room temperature for 1 h. After quenching with water (30 mL), the aqueous layer was extracted with diethyl ether (3×25 mL), and the combined organic layers were washed sequentially with water (2×25 mL) and dried over sodium sulfate. The solvent was removed by vacuum and the crude product was purified by short silica gel column chromatography (2:1, hexane–EtOAc, R_f=0.80). Recrystallization from CH_2Cl_2–Et_2O (1:3, 8 mL) gave **14** (742 mg, 90%), pale yellow needle, mp 134–135 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (d, J_{23}=3.0 Hz, 1H, H_2), 8.20 (d, J_{32}=3.0 Hz, 1H, H_3), 7.60 (d, J_{57}=2.0 Hz, 1H, H_5), 7.79 (d, J_{75}=2.0 Hz, 1H, H_7), 3.07 (s, 3H, SCH_3), 3.05 (s, 3H, SCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.2, 142.6, 141.6, 135.0, 129.6, 128.9, 124.6, 124.1, 121.0, 15.5, 14.3; IR (KBr, cm^{-1}) ν_{max} 3500, 1650, 1587, 1549, 1459, 1430, 1390, 1371, 1311, 1238, 1087, 989, 964, 921, 881, 860, 825, 781, 698, 605. Anal. Calcd for $C_{11}H_{10}BrNS_2$ (300.24): C, 44.00; H, 3.36. Found: C, 44.03; H, 3.33.

4.11. 6-Bromo-4,8-diiodoquinoline (15) and 6-bromo-8-iodoquinoline (16)

n-Butyllithium (4 mL, 1.6 M, 6.03 mmol, 2.2 equiv) was added to a vacuum-dried flask containing tribromide **3** (1 g, 2.74 mmol) in THF (25 mL) at −78 °C. After the mixture was stirred for 90 min, vacuum-dried iodine (1.78 g, 7 mmol) and THF (7 mL) were added. The mixture was stirred at −78 °C for 30 min and then at room temperature for 1 h. After quenching with saturated sodium thiosulfate (50 mL), the aqueous layer was extracted with diethyl ether (3×20 mL), and the combined organic layers were washed sequentially with water (30 mL) and dried over sodium sulfate. After evaporation of the solvent, formed products were purified by silica gel column chromatography (EtOAc–hexane, 1:20). Recrystallization from CH_2Cl_2–Hexane gave compounds **16** (220 mg, 46%) and **15** (80 mg, 0.87 mmol, 6%). R_f**16**=0.66, R_f**15**=0.32 (1:4, CH_2Cl_2–hexane), mp**16** 194–196 °C, mp**15** 185 °C (dec).

4.11.1. Compound *15*

Pale yellow needle; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (d, J_{23}=2.0 Hz, 1H, H_2), 8.40 (d, J_{32}=2.0 Hz, 1H, H_2), 8.35 (d, J_{57}=2.7 Hz, 1H, H5), 7.80 (d, J_{75}=2.7 Hz, 1H, H_7); ^{13}C NMR δ (100 MHz, $CDCl_3$) δ 157.2, 144.6, 143.4, 143.2, 130.6, 129.8, 121.6, 104.6, 92.3; IR (KBr, cm^{-1}) ν_{max} 3019, 2401, 1639, 1423, 1214, 1047, 929, 877, 755, 669. Anal. Calcd for $C_9H_4BrI_2N$ (459.85): C, 23.51; H, 0.88. Found: C, 23.64; H, 0.94.

4.11.2. Compound *16*

Yellow needle; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (dd, J_{23}=4.2 Hz, J_{42}=1.6 Hz, 1H, H_2), 8.40 (d, J_{57}=2.6 Hz, 1H, H_7), 8.00 (dd, J_{43}=8.3 Hz, J_{42}=1.6 Hz, 1H, H_4), 7.95 (d, J_{32}=2.6 Hz, 1H, H_5), 7.42 (dd, J_{34}=8.3 Hz, J_{23}=4.2 Hz, 1H, H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.5, 144.1, 135.9, 135.7, 130.1, 129.7, 125.9, 122.7, 119.9; IR (KBr, cm^{-1}) ν_{max} 3037, 2921, 2852, 1716, 1569, 1533, 1454, 1301, 1234, 1174, 1074, 959, 937, 906, 584. Anal. Calcd for C_9H_5BrIN (333.95): C, 32.37; H, 1.51. Found: C, 32.40; H, 1.38.

4.12. Synthesis of 4,6,8-trimethoxyquinoline (17)

Freshly cut sodium (0.28 g, 12.3 mmol) was added under nitrogen gas to dry methanol (12 mL). When dissolution was completed, the warm solution was diluted with dry dimethylformamide then vacuum-dried cuprous iodide (0.39 g, 1.37 mmol) was added. After dissolution, 4,6,8-tribromoquinoline (**3**) (0.5 g, 1.37 mmol) in dry DMF (12 mL) was added. The reaction mixture was stirred magnetically under a nitrogen gas atmosphere and heated at reflux (ca. 100 °C) for 48 h. The reaction's progress was monitored by TLC and the starting material was consumed. After cooling to room temperature, H_2O (50 mL) and chloroform (70 mL) were added to the reaction mixture. The organic layers were separated, washed with H_2O (2×20 mL), and dried over sodium sulfate. The solvent was removed and the crude product was passed through a short column packed with silica gel (5 g). Recrystallization from a mixture of CH_2Cl_2 and hexane (1:1) at room temperature yielded 4,6,8-trimethoxyquinoline (**17**) (0.18 g, 60%), colorless solid, mp 115–116 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (d, J_{23}=2.7 Hz, 1H, H_2), 7.18 (d, J_{23}=2.7 Hz, 1H, H_3), 6.50 (d, J_{57}=2.4 Hz, 1H, H_7), 6.40 (d, J_{57}=2.4 Hz, 1H, H_5), 3.97 (s, 3H), 3.89 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 156.8, 154.6, 140.4, 132.0, 131.4, 112.4, 99.1, 96.9, 56.4, 55.8, 55.8; IR (KBr, cm^{-1}) ν_{max} 3002, 2960, 2937, 2841, 1617, 1581, 1502, 1453, 1385, 1214, 1160, 1133, 1050, 1029, 869, 827, 782. MS (EI, 70 eV) 219, 218, 190, 188, 175, 160. HRMS (EI) calcd for $C_{12}H_{13}NO_3$ (M^+): 219.0882, found: 219.0884.

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Supplementary data

^{1}H and ^{13}C NMR spectra for selected compounds (15 pages) are provided. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.08.018.

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