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Activation of 6-bromoquinoline by nitration: synthesis of morpholinyl and piperazinyl quinolines

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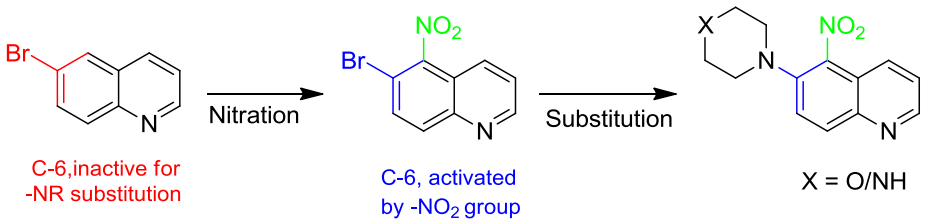
Abstract

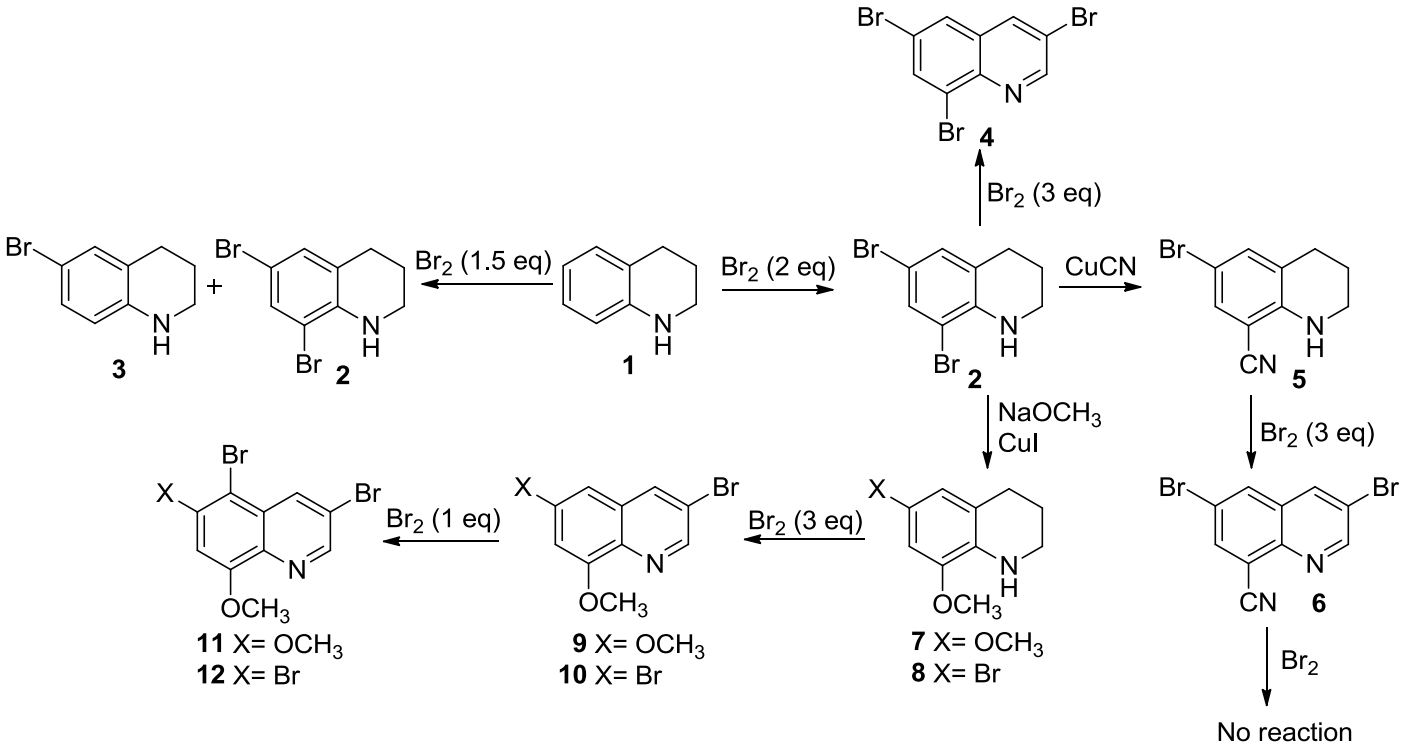
Quinoline forms the key skeletal component of a number of important natural products and pharmacologically-active compounds. Despite a tremendous amount of research pertaining to the derivatization of quinoline, very few general synthetic routes are described in the literature starting from quinoline or tetrahydroquinoline. A simple and convenient method for the polyfunctionalization of quinolines via nitration of bromoquinolines has been developed. This method represents a new synthetic approach to convert brominated nitroquinoline derivatives into useful cyclic amines via nucleophilic-substitution (S_NAr) reaction.



Keywords: Nitration, N-oxidation, 6-bromoquinoline, aminoquinoline, quinoline N-oxides, morpholinyl and piperazinyl quinolines

Introduction

We have recently explored a new synthetic strategy for the synthesis of 6,8-dibromo-1,2,3,4-tetrahydroquinoline (**2**), 6-bromo-1,2,3,4-tetrahydroquinoline (**3**) and 3,6,8-tribromoquinoline (**4**) based on the bromination reaction of substituted or unsubstituted 1,2,3,4-tetrahydroquinolines (**1**), good starting materials with functionality on both rings of quinoline. [1-2] The direct halogenation of quinoline and tetrahydroquinoline seems the most attractive, however, it is still a challenging strategy as haloquinolines are also the best precursors of many other derivatives. In our previous publications, brominated tetrahydroquinolines were transformed into their respective derivatives (Scheme 1).[3-4] Bromination of cyano- and methoxy- 1,2,3,4-tetrahydroquinoline (**5**, **7**, and **8**) gave their corresponding 3-brominated quinoline derivatives (**6,** and **9**-**12**, respectively) (Scheme 1).[4-5] We found that methoxy 1,2,3,4-tetrahydroquinolines (**7**, **8**) were brominated not only at the C-3, but also at the C-5 positions, to give the corresponding bromoquinolines.[5]



Scheme 1. Functionalization of substituted quinolines *via* bromination.

The quinoline moiety forms the key skeleton of several natural-product and pharmacologically-active compounds, displaying a broad spectrum of biological activities.[6–9]

We have investigated a new strategy for the polyfunctionalization of quinolines via nitration of bromoquinolines due to the fact that the nitro group has commonly activated adjacent bromo groups for nucleophilic substitution. Nitro groups are also good starting groups for amine formation.

6-Bromo-5-nitroquinoline (**14**) (DIE-17) exhibits high anti-proliferative, cytotoxic and apoptotic effects on several cancer-cell lines.[10] Therefore, we planned to construct derivatives of (**14**) by simple substitution of the bromine with hetrocyclic rings. This substitution procedure would enable the introduction of heteroatoms via an S_NAr method due to the activation of bromine group on the quinoline core by the nitro group, due to its

strong electon-withdrawing effect, which could lead to other potentially bioactive molecules. e.g., (**17**) and (**18**) (Scheme 3).

It is evident from the literature that quinoline *N*-oxide assists bromination and nitration reactions at the C-2 and C-4 positions.[11] Halogenation at C-2 and nitration at C-4 or C-5[12] *via* the corresponding *N*-oxides provides an important alternative route because 2-, 4-, and 5-substituted quinolines with N-functionality are common themes in pharmacologically-active molecules. This led us to focus on the synthesis of bromo- and nitro-derivatives of quinolines at the C-2, C-4 and C-5 positions.

Although the piperazine- and morpholine-substituted quinolines have a wide range of biological importance,[13-14] the available literature lacks syntheses of these piperazine- and morpholine-based derivatives on the benzene ring of quinolines by substitution methods.

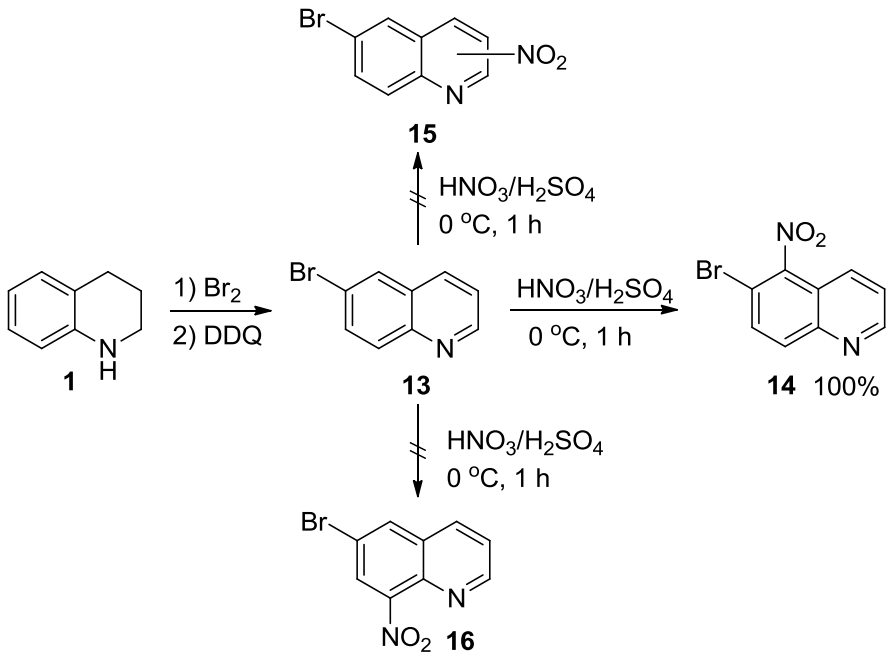
Herein we report our prelimenary results for the synthesis of morpholine-, piperazine- and amino-substituted quinolines starting from 6-bromo-5-nitroquinoline (**14**) and N-oxide derivatives. The work presented is a continuation of our ongoing research and focuses on the synthesis of polyfunctional quinolines, starting from bromoquinolines. We are also interested in the biological activity and structure-activity relationship (SAR) of the synthesized compounds as many quinoline derivatives have exhibited promising pharmacological activities.[7, 15-18]

Results and Discussion

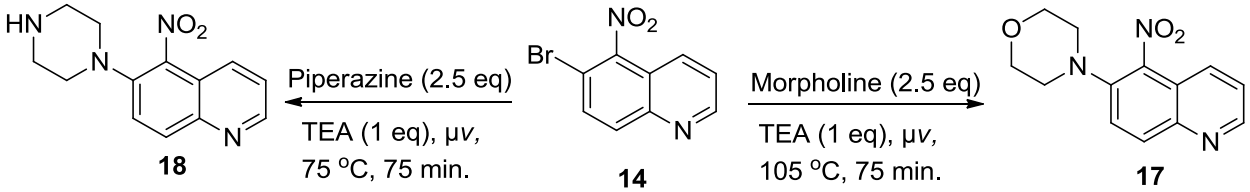
6-Bromoquinoline (**13**) was synthesized according to our previously reported procedures, starting from 1,2,3,4-tetrahydroquinoline (**1**) (Scheme 1).[1] Following nitration using a mixture of HNO_3/H_2SO_4 at 0°C for one hour with stirring, (**13**) yielded 6-bromo-5-nitroquinoline (**14**) as the sole product in quantitative yield (Scheme 2). Actually, nitration of quinoline can lead to a multiplicity of products as also shown in Scheme 2. The reaction proceeded smoothly, however, to selectively give (**14**). The nitro-group substituent results in activation of the bromine group in substitution reactions due to the electron-accepting nature of the nitro group. The -*R* effect of the -NO_2 group favours the substitution reactions with bromine. Previously, our group has reported the synthesis of 6-bromo-5-nitroquinoline (**14**) and its biological activity as an abstract at the Third International Molecular Biology and Biotechnology Congress.[10] 6-Bromo-5-nitroquinoline (**14**) (DIE-17) exhibits high antiproliferative, cytotoxic and appoptotic effects on several cancer cell lines. Synthesis of the compound was also later reported by Chuang *et al.*[20]

After selective synthesis of 6-bromo-5-nitroquinoline (**14**) and its successful isolation and characterization, (**14**) was subjected to nucleophilic-substitution reactions with morpholine and piperazine in microwave-assisted reaction conditions (Scheme 3). Activation of the benzene ring by introduction of the –NO_2 group facilitated the subsequent substitution of the adjacent bromine atom by morpholine and piperazine due to its resulting electron- deficiency effect on the quinoline ring.

6-Bromo-5-nitroquinoline was treated with morpholine or piperazine in triethylamine under microwave conditions (150 W at 90-120 °C) which furnished morpholinyl (**17**) and piperazinyl (**18**) quinolines in high yields (98% and 87%, respectively).



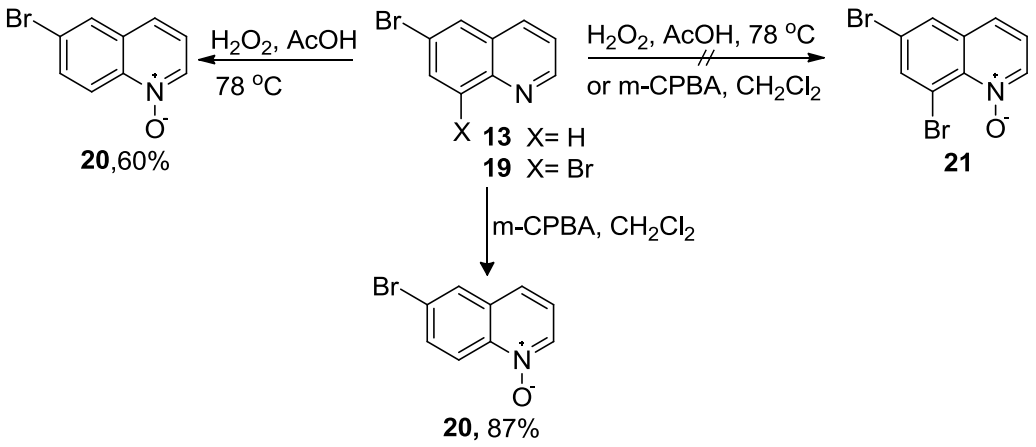
Scheme 2. Synthesis of (**14**) and possible other products of the nitration of (**13**).



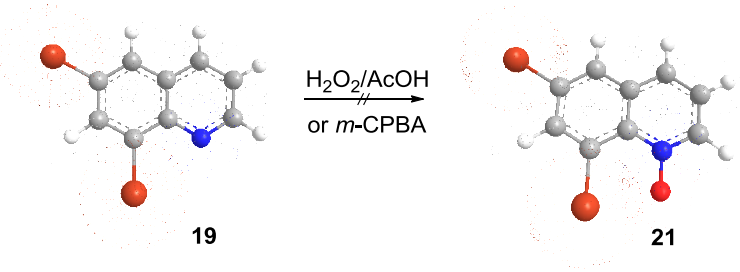
Scheme 3. Synthesis of morpholinyl- (**17**) and piperazinyl- (**18**) quinoline derivatives.

The formations of (**17**) and (**18**) were confirmed by ^{1}H and ^{13}C NMR spectral data. The appearance of aliphatic triplets in the ^{1}H NMR spectra of compound (**17**) (3.85 and 3.20 ppm, ^{3}J 4.5 Hz) and (**18**) (3.21 and 3.05 ppm, ^{3}J 4.5 Hz) confirmed that morpholine and piperazine had replaced the bromine atom at C-6. The additional singlet of N-H appears at 2.51 ppm in compound (**18**). The rest of the NMR spectrum is quite similar to that of the reactant (**14**) with a doublet for H-2 at 8.87 ppm (^{3}J 4.0 Hz), and doublets for H-7 and H-8 at 7.62 and 8.19 ppm (^{3}J 9.0 Hz), respectively. The aromatic-region doublet of doublets at δ_H 7.51 ppm ($J_{3,2}$ 8.5 Hz, $J_{3,4}$ 4.0 Hz) belongs to H-3. The appearance of two aliphatic (52.3 and 46.1 ppm) and nine aromatic carbons in ^{13}C NMR further confirmed the proposed structure of (**18**).

To afford the 2- and 4-nitro-substituted-bromoquinoline derivatives (**22**) and (**23**), it was first attempted to convert bromoquinolines (**13**) and (**19**) into the quinoline *N*-oxides (**20**) and (**21**), respectively (Scheme 4). which facilitated the nitration at the pyridine ring of the quinoline moiety due to +R effect of the *N*-oxide form. The *N*-oxidations of 6-bromo (**13**) and 6,8-dibromoquinoline (**19**) were carried out in the presence of AcOH/H_2O_2 or *m*-CPBA (Scheme 5). Both AcOH/H_2O_2 and *m*-CPBA reacted smoothly with (**13**) and afforded the *N*-oxide derivative (**20**) in good yield (60% and 87%, respectively). Several attempts to effect the same results for the *N*-oxidation of (**19**) to yield (**21**) failed, however, under the same or similar conditions. These attempts resulted in polymeric materials instead of the expected product. It is thought that the unsuccessful formation of the *N*-oxide (**21**) may have been the result of steric-hindrance effects of the bulky bromine group at C-8 (Scheme5).



Scheme 4. N-oxidation reactions of bromoquinolines (**13**) and (**19**).



Scheme 5. Molecular models showing the possible steric-hindrance effect of the C-8 Br group in the attempted formation of 6,8-dibromoquinoline-1-oxide (**21**).

The ^{1}H and ^{13}C NMR spectra of the 6-bromoquinoline-1-oxide (**20**) are quite similar to those of 6-bromoquinoline (**13**) with a little upfield shift of the aromatic protons of the pyridine ring and H-8. The signal of H-5 is a doublet at δ_H 8.06 (2.5 Hz, meta coupling). The upfield shift of H-2 of (**20**) compared with starting material (**13**), as expected, appears at 8.56 ppm as a doublet (6.0 Hz). Due to the ɣ-gauche effect of the *N*-O group, the signal of H-8 shifts downfield (8.63 ppm, 9.2 Hz) (Figure 1).

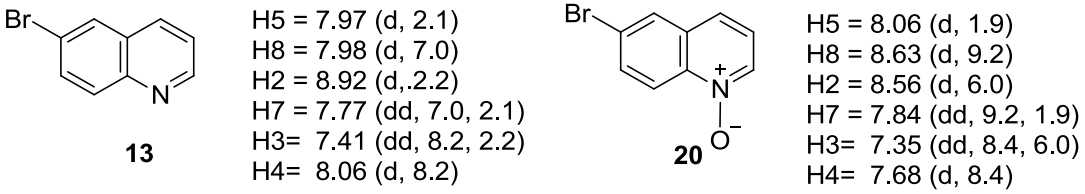
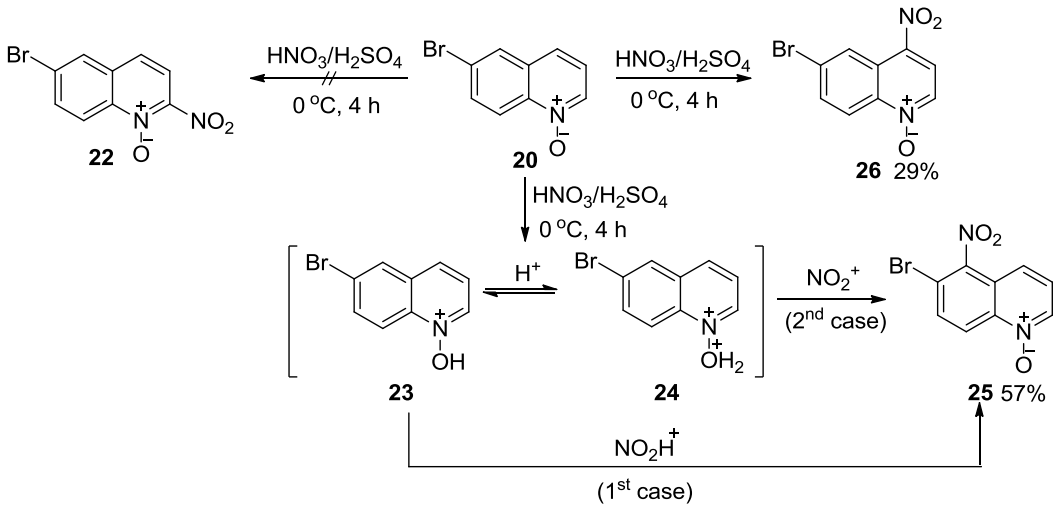


Figure 1. ^{1}H NMR values of compound (**20**) and its starting material (**13**).

Bromination of 6-bromoquinoline-1-oxide (**20**) has recently been reported.[11] Therefore, we focused on the nitration of 6-bromoquinoline-1-oxide (**20**). The slow addition of a mixture of HNO_3/H_2SO_4 to an ice-chilled solution of (**20**) provided a mixture of 5-nitro-6-bromoquinoline-1-oxide (**25**) and 4-nitro-6-bromoquinoline-1-oxide (**26**). The products were isolated by column chromatography in yields of 57% and 29%, respectively (Scheme 6).



Scheme 6. Results of nitration of 6-bromoquinoline-1-oxide (**20**)

The proposed mechanism for the synthesis of (**25**) and (**26**) is represented in Scheme 6. In highly acidic conditions, strong nitrating agents prefer selectively the C-5 position on quinoline *N*-oxide. The reasons for the regioselectivity may be explained in two ways. First, the protonated nitronium ion contributes to regioselectivity at C-5 or the deprotonated quinoline-1-oxide (**20**) (Scheme 6).[20-21] Alternatively, regioselectivity at C-5 may occur due to electrostatic repulsion between the electrophile and the positive charge of the oxonium ion of the 6-bromoquinoline *N*-oxide (**24**) (Scheme 6).[21] Some of the *N*-oxide molecules are probably not protonated at low temperatures. For that reason, non-protonated *N*-oxides were nitrated at C-4 in a small ratio.

The structures of **25** and **26** were characterized by FT/IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis. X-ray crystallography was also performed for **25**. In the ^{1}H NMR spectra of **25** and **26**, the disappearance of the doublets of H-5 and H-4 from starting compound **20** was good evidence for the formations of **25** and **26**, respectively. In the ^{1}H NMR spectra of **25**, signals of H-8 and H-2 were observed downfield, having similar chemical-shift values as the starting molecule **20**, while the signal of H-7 (δ 7.96) was observed more downfield due to the *NO$_2$* group in **25** (Figure 2).

In the ^{1}H NMR spectrum of 4-nitro-6-bromoquinoline-1-oxide (**26**), H-5 (J_{57} 2.0 Hz) shifted more downfield (δ_H 9.11) due to the gamma gauche effect of the *NO$_2$* group bonded at C-4 (Figure 2). While H-7 gave a doublet of doublets signal (^{3}J 9.3 and ^{4}J 2.0 Hz) at 7.96 ppm, the doublet signal of H-3 (^{3}J 6.9 Hz) at 8.26 ppm was shifted more downfield compared to the signal of H-3 (δ 7.35, ^{3}J 8.4 and 6.0 Hz) of starting material **20**. This evidence indicated that a *NO$_2$* group was bonded to 6-bromoquinoline-1-oxide (**20**) at the C-4 position.

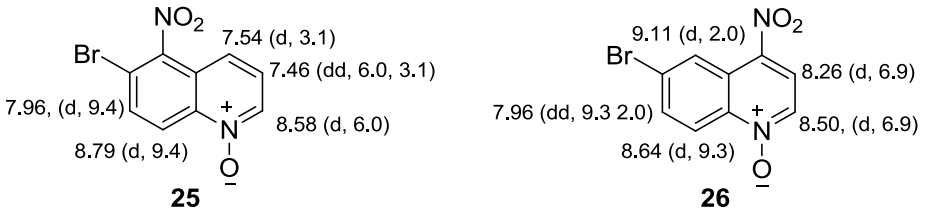
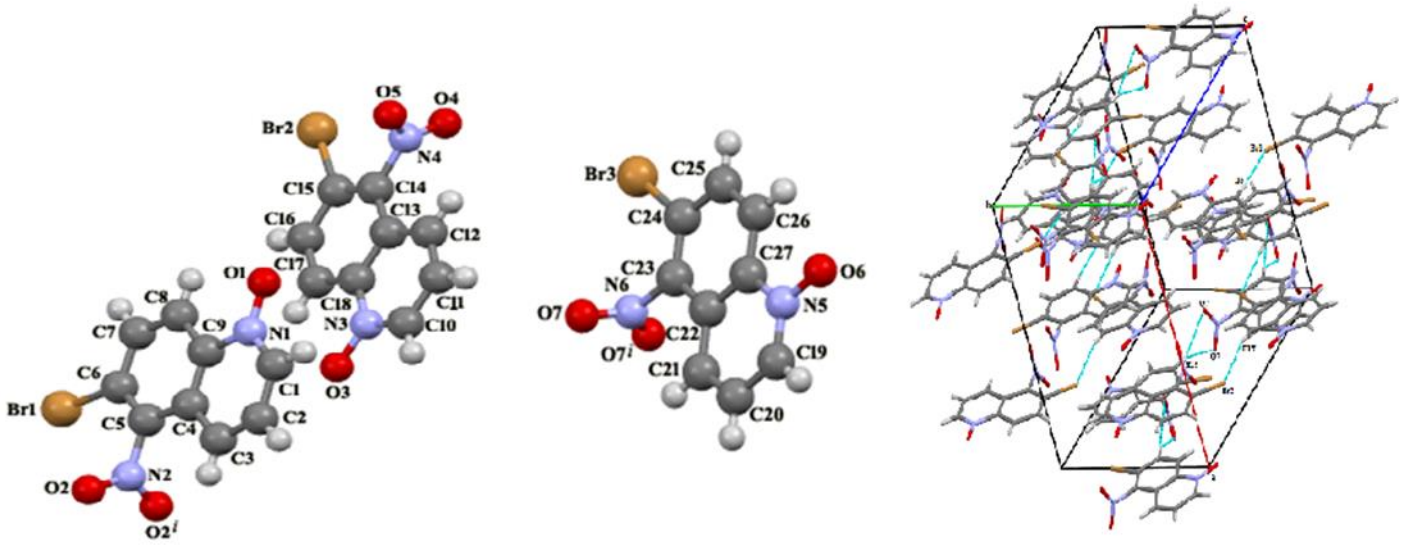


Figure 2. ^{1}H NMR values and coupling constants of 5-nitro-6-bromoquinoline-1-oxide (**25**) and 4-nitro-6-bromoquinoline-1-oxide (**26**).

The structure of compound **25** was confirmed by X-ray diffraction studies (Table 1 and Figure 3). The dihedral angle between pyridine rings (C1-C4/C9/N1 and C19-C22/C27/N5) and phenyl rings (C4-C9 and C22-C27) for (I) and (III) is 0°. The dihedral angle between pyridine rings [(C10-C13/C18/N3) with a maximum deviation of 0.0062(1) Å for C18] and phenyl rings [(C13-C18) with a maximum deviation of 0.0068(1) Å for C16] is 0.80° for (II). The C-N, C-Br, and N-O bond distances [1.315(13), 1.488(11), 1.861(9), 1.277(10), and 1.197(6) Å for (I); 1.330(10), 1.480(8), 1.889(7), 1.310(8), and 1.213(8) Å for (II); and 1.325(12), 1.482(11), 1.898(8), 1.299(10), and 1.167(7) Å for (III), respectively, are the most sensitive indicators of the formation of **25**. The carbon-carbon, carbon-nitrogen, and nitrogen-oxygen bond lengths in compound **25** are comparable with those reported for a similar structure.[22] Interesting intermolecular C-H…Br and C-H…O interactions are observed in the crystal structure of **25** (Figure 3). All bond lengths are provided in the supporting material.

Table 1. Selected crystal data and structure-refinement parameters for **25**

Crystal data and structure- refinement parameters			
Identification code	**25**	**Identification code**	**25**
Crystal system	Orthorhombic	μ (mm^{-1})	4.422
Space group	$Pmc2_1$	ϑ range (º)	2.886-28.337
a (Å)	13.6694(13)	Measured refls.	78841
b (Å)	9.6036(10)	Independent refls	4108
c (Å)	14.1177(16)	R_{int}	0.0464
V (Å^3)	1853.3(3)	*S*	1.221
Z	8	*R1/wR2*	0.0448/0.0751
D_c (g cm^{-3})	1.929	$\Delta\rho_{max}/\Delta\rho_{min}$ (eÅ^{-3})	0.624/-0.737



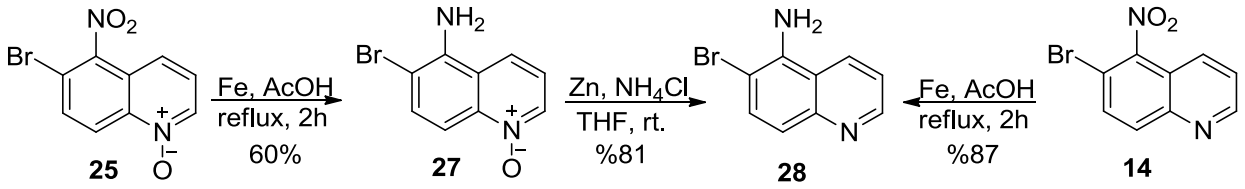
a **b** **c**

Figure 3. ORTEP diagram of **25** (**a** and **b**); Crystal packing diagram of **25** (**c**).

Nitroquinolines are good precursors for amino-group derivatives. For this reason, the metal-based reduction of **25** was carried out in the presence of acetic acid. The reduction was performed by adding powdered metal (Fe) to the solution of **25** in *aq.* AcOH. After the addition of the metal, the mixture was stirred at 60 °C until the reactant disappeared on TLC. The extraction and normal work-up afforded **27** in 60% yield (Scheme 7).

We have also explored the deoxygenation of aromatic *N*-oxides using zinc dust (Scheme 7). The mixture of zinc and ammonium chloride in THF provides the mild conditions which furnished 5-amino-6-bromoquinoline (**28**) in high yield (81%). The synthesis of 5-amino-6-bromoquinoline by reduction of 5-nitro-6-bromoquinoline (**14)** is already available in the literature, but in lower yield (68%) as compared to our results.

The ^{1}H NMR spectrum of amino-substituent product **27** consists of the same signals with a shift upfield due to the electron-donating feature of the *NH*$_2$ group. The successful reduction was inferred from the ^{1}H NMR spectrum showing a broad singlet of the two -*NH*$_2$ protons. Moreover, the disappearance of an absorption signal of *N*=O and appearance of a new signal of *N-H* stretching vibrations at 3420 cm^{-1} in the IR spectrum also provide clear evidence of formation of the reduced product **28**. The spectral values (^{1}H, ^{13}C NMR and IR) of 5-amino-6-bromoquinoline (**28**) corresponded with those in the literature.[19]



Scheme 7. Reduction reactions of **25** using Fe and of **27** using Zn.

Conclusions

A simple and convenient method for the polyfunctionalization of quinolines via nitration of bromoquinolines has been developed. This represents a new synthetic approach to convert brominated nitroquinoline derivatives into useful cyclic amines by nucleophilic-substitution (S_NAr) reactions. We have developed a selective route for the synthesis of both 6-substituted morpholine and piperazine quinolines containing nitro substituents at the C-5 positions that could be converted to amino groups. The compounds exhibit high biological activities.[23] 5-Nitro-6-bromoquinoline was found to be highly reactive towards S_NAr nucleophilic substitution and investigations are ongoing regarding the generality and application of this approach to other bromoquinoline derivatives. On the other hand, the activation of the quinoline ring at different positions to obtain novel quinoline derivatives was enabled by *N*-oxidation of 6-bromoquinoline using *m*-CPBA.

Experimental Section

General. Thin-layer chromatography was carried out on Merck silica F_{254} 0.255-mm plates, and spots were visualized by UV at 254 nm. Flash column chromatography was performed using Merck 60 (70-230 Mesh) silica gel. The microwave reactions were run in a CEM Discover Labmate instrument. Melting points were determined on a Thomas Hoover Capillary Melting Point Apparatus. Solvents were removed under reduced pressure. IR spectra were recorded on a Jasco 430 FT/IR instrument. High-resolution Mass spectra (HRMS) were recorded on a mass spectrometer under electron-impact (EI) and chemical-ionization conditions. Elemental analysis was recorded on an Elementar Vario MICRO Cube instrument. NMR spectra were recorded on a Bruker 500 MHz for ^{1}H and at 125 MHz for ^{13}C NMR.

Synthesis of 6-Bromo-5-nitroquinoline (14). 6-Bromoquinoline (**13**) (0.190 g, 0.932 mmol) was dissolved in 4 mL of sulphuric acid, and cooled at -5 °C with a salt-ice bath. A mixture of H_2SO_4 (1.5 mL) and HNO_3 (1.5 mL) acid was prepared and the acid mixture was cooled at -5 °C. The solution obtained was cooled at 0 °C on a salt-ice bath. While the 6-bromoquinoline (**13**) solution was stirred with a magnetic stirrer, the H_2SO_4 / HNO_3 mixture was added dropwise with the aid of a Pasteur Pipette within one hour so the solution temperature did not exceed 0 °C. The dark brown color of the reaction solution turned into a dark yellow color. After one hour the reaction was compete. The reaction mixture was poured over crushed ice (20 g) in a beaker. After the ice melted, the mixture was extracted with CH_2Cl_2 (5 × 5 mL). The organic phase was neutralized with a $NaHCO_3$ (10%) solution and dried over Na_2SO_4. The solvent was removed in-vacuo. Yellow-colored needle crystals were obtained as the sole product in quantitative yield (0.23 g). mp 128-130 °C. IR (solid KBr, *v*max, cm^{-1}): 3050, 3019, 2953, 2918, 2850, 1563, 1486, 1414, 1387, 1351, 1318, 1145, 1045, 831, 807, 755. ^{1}H NMR (500 MHz, ppm, $CDCl_3$): δ_H 9.05 (1H, dd, $J_{2,3}$ 4.2 Hz,$J_{2,4}$ 1.6 Hz, H-2)**,** 8.15 (1H, d, $J_{7,8}$ 9.0 Hz, H-7), 8.05 (1H, d, $J_{4,3}$ 8.6 Hz, H-4), 7.92 (1H,d, $J_{8,7}$ 9.0 Hz, H-8), 7.61 (1H, dd, $J_{3,4}$ 8.6 Hz; $J_{3,2}$ 4.2 Hz, H-3). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 152.1, 146.6, 133.3, 132.9, 129.8, 123.8, 123.4, 121.4, 112.2 Anal. calcd for $C_9H_5BrN_2O_2$ (251.95): C, 42.72; H, 1.99; N, 11.07. Found: C, 42.54; H, 2.03; N, 11.12.

Synthesis of 5-nitro-6-(morpholin-1-yl)quinoline (17). A mixture of 6-bromo-5-nitroquinoline (**14**) (0.1 g, 0.395 mmol), morpholine (0.103 g, 1.185 mmol) and triethylamine (0.040 g, 0.395 mmol) was heated slowly to 80 °C over 30 min while stirring. The open reaction vessel was placed into the microwave cavity. Microwave irradiation of 150 W was used and the temperature was ramped from room temperature to the desired temperature of 90-119 °C. The reaction mixture was stirred continuously under microwave irridation at an average of 105 °C for 45 min. The reaction mixture was cooled to room temperature and taken up in CH_2Cl_2 (15 mL). The organic layer was washed with 5% aq $NaHCO_3$ (40 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The crude product was filtered by a short silica gel column eluted with a mixture of n-hexane/EtOAc (1:1) to afford the desired yellow solid product (116 mg, 98% yield). mp 95-97 °C. IR (solid KBr, *v*max, cm^{-1}): 2967, 2916, 2895, 2854, 1738, 1620, 1589, 1341, 1262, 1211, 1068, 869, 815, 780, 731. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 8.90 (1H, dd, ^4J 1.5 Hz; 4.5 Hz, H-2), 8.21 (1H, d, ^3J 9.0 Hz, H-4), 8.06 (1H, d, ^3J 9.0 Hz, H-8), 7.63 (1H, d, ^3J 9.0 Hz, H-7), 7.53 (1H, dd, ^3J 9.0 Hz; 4.5 Hz, H-3), 3.85 (4H, t, ^3J 4.5 Hz), 3.20 (4H, t, ^3J 4.5 Hz).^{13}C NMR (125 MHz, $CDCl_3$): δ_C150.0, 144.1, 142.2, 139.9, 133.5, 129.5, 123.8, 123.4, 121.5, 66.7, 51.8. HRMS for ($C_{13}H_{13}N_3O_3$ $[M+H]^+$) (ESI,*m/z*). Calcd: 260.0994. Found: 260.1035

Synthesis of 5-nitro-6-(piperazin-1-yl)quinoline (18). A mixture of 6-bromo-5-nitroquinoline (**14**) (0.118 g, 0.446 mmol), piperazine (0.115 g, 1.39 mmol), and triethylamine (0.045 g, 0.446 mmol) was heated slowly to 80 °C over 30 min while stirring. The open reaction vessel was placed into the microwave cavity. Microwave irradiation of 150 W was used and the temperature ramped up from room temperature to the desired temperature of 68-78 °C. The reaction mixture was stirred continuously under microwave irradiation at average 74 °C for 45 min. The reaction mixture was cooled to room temperature and taken up in CH_2Cl_2 (25 mL). The organic layer was washed with 5% aq $NaHCO_3$ (50 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The crude product was filtered by a short silica gel column eluting with MeOH to afford the brown oil product (87%; 0.100 g). R*f* 0.19 (MeOH). IR (solid KBr, *v*max, cm^{-1})**:** 3320, 2836, 1620, 1513, 1495, 1343, 1248, 1138, 1014, 978, 831, 795, 770, 541. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 8.87 (1H, d, ^3J 4.0 Hz, H-2), 8.19 (1H, d, ^3J 9.0 Hz, H-8), 8.06 (1H, d, ^3J 8.5 Hz, H-4), 7.62 (1H, d, ^3J 9.0 Hz, H-7), 7.51 (1H, dd, ^3J 8.5 Hz,^3J 4.0 Hz, H-3), 3.21 (4H, t, ^3J 4.5 Hz), 3.05 (4H, t, ^3J 4.5 Hz), 2.51 (1H, s, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 149.7, 143.8, 142.8, 139.1, 133.4, 129.4, 124.2, 123.4, 121.6, 52.3, 46.1. HRMS for ($C_{13}H_{14}N_4O_2$[M+H]$^+$) (ESI, *m/z*). Calcd: 259.1195. Found: 259.1157.

Synthesis of 6-bromoquinoline-1-oxide (20). Method A: To a solution of 6-bromoquinoline (**13**) (0.32 g, 1.54 mmol) in acetic acid (20 mL), hydrogen peroxide (2 mL) was added and stirred in an oil bath at reflux temperature for 2 h. The reaction was monitored by thin layer chromatography (TLC) until consuming starting material. The solution was cooled at room temperature and diluted with distilled water (30 mL). The pale yellow mixture was cooled to -5 °C with mixture of salt and ice. The mixture was neutralized by adding a solution of Na_2CO_3 (10%) and extracted with CH_2Cl_2 (2 × 25 mL). The organic layer was dried over Na_2SO_4 and filtered. The solvent was evaporated to dryness under reduced pressure. A yellow solid was obtained (0.20 g, 60%). R*f*: 0.07 (3:1; EtOAc/ hexane).

Method B: To a solution of 6-bromoquinoline (**13**) (0.73 g, 3.26 mmol) in cooled CH_2Cl_2 (43 mL), *m*-chloroperbenzoic acid (1.21 g, 7 mmol) was added and stirred at room temperature overnight. The reaction was monitored by TLC. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and extracted with KOH (6 N, 3 × 15 mL). The organic layer was dried over Na_2SO_4 and filtered. The solvent was evaporated to dryness under reduced pressure. A yellow solid, 0.69 g, (87%) was obtained. R*f* 0.15 in EtOAc. mp 131-133 °C. IR (solid KBr, *v*max, cm^{-1}): 3289, 3092, 3067, 2920, 2850, 1560, 1590, 1142, 1064, 776, 732. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ_H 8.63 (1H, d, ^3J 9.2 Hz, H-8), 8.56 (1H, d, ^3J 6.0 Hz, H-2), 8.06 (1H, d, ^4J 1.9 Hz, H-5), 7.84 (1H, dd, ^3J 9.2, ^4J 1.9 Hz, H-7), 7.68 (1H, d, ^3J 8.4 Hz, H-4), 7.35 (1H, dd, ^3J 8.4, ^3J 6.0 Hz, H-3). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 140.0, 135.9, 133.9, 131.6, 130.1, 125.0, 123.3, 122.2, 121.8. Anal. calcd for C_9H_6BrNO (222.96): C, 48.25; H, 2.70; N, 6.25. Found: C, 48.12; H 2.83; N, 6.32.

Nitration of 6-bromoquinoline-1-oxide (20). To the solution of 6-bromoquinoline-1-oxide (**20**) (1 eq, 0.6 g, 2.67 mmol) in H_2SO_4 (5 mL) at 0 °C, HNO_3 (3 eq, 0.8 mL) was added drop-wise and stirred for 4 h. The reaction mixture was poured onto ice and filtered. The solid mass was washed with H_2O (3 × 10 mL) and the crude product purified by column chromatography. The elution with 5% EtOAc in *n*-hexane (250 mL) afforded 4-nitro-6-bromoquinoline 1-oxide (**26**) (0.21 g, 29%) as a yellow powder, and, with crystallization with 8% EtOAc in *n*-hexane (500 mL), furnished 5-nitro-6-bromoquinoline 1-oxide (**25**) (0.41 g, 57%).

6-Bromo-5-nitroquinoline 1-oxide (**25**) Yellow needles, 0.41 g (57%), R*f* 0.30 (EtOAc/hexane 3:7). mp 204-206 °C. IR (solid KBr, *v*max, cm^{-1}): 3050 (aromatic C-H), 1480 (N-O), 700 (C-Br). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.46 (1H, dd, ^3J 6.0 Hz, ^3J 3.1 Hz, H3), 7.54 (1H, d, ^3J 3.1 Hz, H4), 7.96 (1H, d, ^3J 9.4 Hz, H7), 8.58 (1H, d, ^3J 6.0 Hz, H2), 8.79 (1H, d, ^3J 9.4 Hz, H8); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 147.9, 140.6, 136.6, 133.7, 124.3, 124.2, 123.5, 118.6, 115.2. Anal. calcd for $C_9H_5BrN_2O_3$ (267.95): C, 40.18; H, 1.87; N, 10.41. Found: C, 40.28; H 1.83; N, 10.52.

6-Bromo-4-nitroquinoline 1-oxide (26). Yellow powder (0.21 g, 29%). mp 214-215 °C. R*f* 0.68 (EtOAc /hexane 3:7). IR (solid KBr, *v*max, cm^{-1}): 2995 (aromatic C–H), 1537 (N-O), 730 (C-Br). ^{1}H NMR (500 MHz, $CDCl_3$,): δ_H 7.96 (1H, dd, ^3J 9.3, ^4J 2.0 Hz, H-7), 8.26 (1H, d, ^3J 6.9 Hz, H-3), 8.50 (1H, d, ^3J 6.9 Hz, H-2), 8.64 (1H, d, ^3J 9.3 Hz, H-8), 9.11 (1H, d, ^4J 2.0 Hz, H-5). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 141.7, 138.4, 135.0, 134.3, 127.6, 127.1, 123.5, 122.0, 120.4. Anal. calcd for $C_9H_5BrN_2O_3$ (267.95): C, 40.18; H, 1.87; N, 10.41. Found: C, 40.28; H 1.83; N, 10.52.

Synthesis of 5-amino-6-bromoquinoline-1-oxide (27). To the stirring solution of 5-nitro-6-bromoquinoline 1-oxide (**25**) (1 eq, 122 mg, 0.045 mmol) in H_2O (10 mL), and one drop of CH_3COOH (0.1 mL) the powdered Fe (6 eq, 15.1 mg, 0.27 mmol) was added and refluxed for 3 h. The flask was removed and cooled to room temperature. The mixture was diluted with water (30 mL), extracted with EtOAC (3×10 mL), dried over *anhydrous* Na_2SO_4 (5 g), filtered, and the solvent was removed to afford the crude product (100 mg) which, upon further crystalization in CH_2Cl_2 (5 mL), furnished the titled compound (**27**) as needle-like crystals. White needles (65 mg, 60%), R_f 0.35 (EtOAc/hexane 3:7). mp 162-164 °C. IR (solid KBr, *v*max, cm^{-1}): 3550 (N-H), 3000 (aromatic C-H) 1480 (N-O). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.31 (1H, dd, ^3J 4.0 Hz, ^3J 8.5 Hz, H-4), 7.38 (1H, d, ^3J 9.5 Hz, H-7), 7.64 (1H, d, ^3J 9.0 Hz, H-8), 8.10 (1H, d, ^3J 8.5 Hz, H-3), 8.83 (1H, d, ^3J 4.0 Hz, H-8), 4.65 (s, 2H,

NH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 149.0, 140.9, 135.4, 132.4, 130.2, 120.8,109.7, 104.3, 102.6. Anal. calcd for $C_9H_7BrN_2O$ (237.97): C, 45.22; H, 2.95; N, 11.72. Found: C, 45.28; H 2.98; N, 11.58.

Synthesis of 5-amino-6-bromoquinoline (28). Method A: 6-Bromo-5-nitroquinoline (250 mg, 1.0 mmol, 1.0 eq) was dissolved in CH_3COOH (5 mL). Fe powder (335 mg, 6.0 mmol, 6.0 eq) was added and the reaction heated to approx. 75 °C for 150 min. Upon cooling, the mixture was filtered through filter paper and celite, and extracted with CH_2Cl_2 (3x20 mL) and a solution of 10% aq Na_2CO_3 (3x15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude material was purified by chromatography on silica gel (40% EtOAc/60% hexanes eluant) to provide 5-amino-6-bromoquinoline as a light yellow, amorphous solid (193 mg, 87% yield).

Method B: To a magnetically stirred suspension of the 5-amino-6-bromoquinoline 1-oxide (**20**) (1 eq, 1 mmol, 269 mg) and freshly activated Zinc dust (4 mmol) in THF (2 mL) was added a saturated solution of ammonium chloride (10 mL). The resulting reaction mixture was stirred for 30 min at room temperature. The catalyst was removed by filtration and washed with 5% solution of Na_2CO_3 (10 mL). The organic layer was dried over anhydrous Na_2SO_4. The residue obtained following evaporation of the solvent was purified by column chromatography on silica gel (EtOAc/hexane ; 3:7) to give the amorphous solid (**28**) (190 mg, 1 mmol, 81% yield). IR (solid KBr, *v*max, cm^{-1}): 3423, 3297, 3162, 1635, 1581, 1569, 1457, 1398, 1357, 1323. ^{1}H NMR (500 MHz, $CDCl_3$) : δ_H 8.90 (1H, dd, ^3J 4.5 Hz, ^4J 1.5 Hz, H2), 8.18 (1H, d, ^3J 8.5, H-4), 7.71 (d, ^3J 9.0 Hz, 1H, H-8), 7.44 (d, ^3J 9.0 Hz, 1H, H-7), 7.39 (dd, ^3J 8.5 Hz, ^3J 4.5 Hz, 1H, H-3), 4.70 (s, 2H, NH_2). ^{13}C NMR (125 MHz, $CDCl_3$, in ppm): δ_C 150.3, 148.1, 139.6, 133.3, 129.4, 120.7, 120.2, 118.7, 104.3 (Lit[19]). Anal. calcd for $C_9H_7BrN_2$ (221.98): C, 48.46; H, 3.16; N, 12.56. Found: C, 48.78; H 3.21; N, 12.37.

Crystal structure determination for 6-bromo-5-nitroquinoline-1-oxide (25). A suitable sample of size 0.15 x 0.11 x 0.09 mm was selected for the crystallographic study. All diffraction measurements were performed at room temperature (296°K) using graphite monochromatic MoK_α radiation and a Bruker APEX-II CCD diffractometer. A total of 4795 reflections with [$2.886^o < \vartheta < 28.337^o$] were collected in the rotation mode and cell parameters were determined by using *SAINT* software.[24] The structure was solved by direct methods using *SHELXS-97*.[25]The refinement was carried out by full-matrix least-squares method on the positional and anisotropic temperature parameters of the non-hydrogen atoms,[26] or equivalently corresponding to 311 crystallographic parameters. All non-hydrogen atom parameters were refined anisotropically and all H atom parameters were fixed to 0.93 Å for C-H. The U_{iso} values of H atoms were also fixed to 1.2 times the U_{eq} value of parent atom for C-H. Other data-collection conditions and parameters of refinement process arepresented in Table 1.

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Supplementary Materials

Copies of ^{1}H NMR spectra of compounds **14**, **17**, **18**, **20**, **25**, **26, 27** and **28** and ^{13}C NMR spectra of compounds **14**, **17**, **18**, **20**, **25** and **26** are represented in a Supplementary Materials Addendum.

An X-ray crystallographic file in CIF format, for the structure of compound **25** CCDC: 1525693 has been deposited with the Cambridge Crystallographic Data Center. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif by e-mailing data requests @ccdc cam.ac.uk. or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0) 1223-33603.

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