

단 신

***N*-Bromosuccinimide로 5,8-Dimethoxyquinoline 화합물의 위치 선택적 브롬화 반응**

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Regioselective Bromination of 5,8-Dimethoxyquinoline with *N*-Bromosuccinimide

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Streptonigrin¹ and lavendamycin² are highly substituted quinoline-5,8-dione antitumor antibiotics³, which have activities against a broad range of tumors, and variously substituted quinoline-5,8-diones were synthesized and tested for their biological activities.^{4,5} Since the chemistry and structure-activity relationships of the substituted quinoline-5,8-diones are major concerns of the previous reports, 7-bromoquinoline-5,8-dione is chosen as one of key intermediates to allow introduction of structural diversity. However, there are few examples of its preparations in the literature. Previously, for example, both 6-bromoquinoline-5,8-dione and 7-bromo analog were directly prepared in low yields (0-15% and 5-18% respectively) from a one-step oxidative bromination⁶ (NBS/AcOH-H₂O) of 8-hydroxyquinoline. So far, the only practical method that leads to 7-bromoquinoline-5,8-dione is a three-step route^{7,8} consisting of (i) regioselective bromination (NBS/THF-cat.H₂SO₄) of 5-nitro-8-hydroxyquinoline at C(7) position, (ii) reduction of the nitro group using Na₂S₂O₄ to the corresponding amine, and (iii) oxidative *p*-quinone formation under rather harsh conditions

(K₂Cr₂O₇-H₂SO₄). Seeking a new and milder route to 7-bromoquinoline-5,8-dione, we selected on the use of 5,8-dimethoxyquinoline 1, a readily available material by the condensation of 2,5-dimethoxyaniline with acrolein. It has not been widely used as a substrate for bromination, which may be due to discouraging results expected in terms of both regioselectivity and further oxidation of the dimethoxy benzene ring. In this study, we describe the high regioselectivity achieved in the monobromination of 1 at C(7) position with NBS in THF, which strongly contrasts with the competing C(6)-bromination observed for the same substrate in other solvent systems. Access to the C(7)-bromo derivative will permit entry into 7-bromoquinoline-5,8-dione by mild oxidation using cerium(IV) ammonium nitrate.

EXPERIMENTAL SECTION

¹H NMR spectra were recorded on a Varian 2000 (300 MHz) spectrometer. MS spectra were recorded with a Micromass Autospec spectrometer. Merck silica gel (230-400 mesh) was employed for flash

column chromatography. Oxidative demethylation product of **2b** exhibited spectral data consistent with the literature report.⁸

Procedure for Preparation of 5,8-Dimethoxyquinoline. Acrolein (5.22 g, 90 mmol) was added dropwise to a refluxing solution of 2,5-dimethoxyaniline (2.75 g, 18 mmol) in 6N HCl (100 mL), and the resulting solution was refluxed for an additional 1 h. The reaction mixture was cooled, diluted with water (200 mL), basified with 10% NaOH solution, and extracted with dichloromethane (3×100 mL). The extract was washed with water, dried, and evaporated. The residue was chromatographed on silica gel (eluting with ethyl acetate-hexane) to afford 1.53 g (Yield 45%).

General procedure for bromination of 5,8-dimethoxyquinoline. To a solution of 5,8-dimethoxyquinoline (380 mg, 2 mmol) in dry solvent (10 mL) chosen from carbon tetrachloride, dichloromethane, acetonitrile and tetrahydrofuran was added *N*-bromosuccinimide (4 mmol). The mixtures were stirred at room temperature for 2 h, and washed with saturated sodium carbonate solution. Upon conventional work-up procedures, the crude reaction mixtures were subjected to column chromatography (silica gel: ethyl acetate-hexane) to isolate the bromination products (**2a** and **2b**).

Procedure for oxidative demethylation of 7-bromo-5,8-dimethoxyquinoline. 7-Bromo-5,8-dimethoxyquinoline (100 mg, 0.37 mmol) was dissolved in 5 mL of acetonitrile. Ceric ammonium nitrate (5 equiv, 1 g, 1.9 mmol) in 5 mL of H₂O was added with stirring and the mixture stirred for 6 hr at room temperature. The reaction mixture was extracted into ethyl acetate, washed with brine, and then dried. The solvent was removed under vacuum and the residue was chromatographed (silica gel: ethyl acetate-hexane) to afford 64 mg (Yield 72%) of 7-bromoquinoline-5,8-dione identical to material previously described.⁸

Spectral data

1: $R_f=0.26$ (1:1 ethyl acetate/hexane): ¹H NMR (CDCl₃, 300 MHz) δ 8.95 (dd, 1H, $J=4.2, 1.8$ Hz, Ar-H), 8.56 (dd, 1H, $J=8.4, 1.8$ Hz, Ar-H), 7.43

(dd, 1H, $J=8.4, 4.2$ Hz, Ar-H), 6.94 (d, 1H, $J=8.4$ Hz, Ar-H), 6.76 (d, 1H, $J=8.4$ Hz, Ar-H), 4.05 (s, 3H, OCH₃), 3.96 (s, 3H, OCH₃); MS (m/z), 189 (M^+ , 34%), 174 (100%).

2a: $R_f=0.30$ (1:1 ethyl acetate/hexane): ¹H NMR (CDCl₃, 300 MHz) δ 8.96 (dd, 1H, $J=4.5, 1.5$ Hz, Ar-H), 8.40 (dd, 1H, $J=8.4, 1.8$ Hz, Ar-H), 7.51 (dd, 1H, $J=8.7, 4.2$ Hz, Ar-H), 7.13 (s, 1H, Ar-H), 4.07 (s, 3H, OCH₃), 3.95 (s, 3H, OCH₃); MS (m/z), 269 (M^+ , 51%), 267 (M^+ , 50%), 252 (100%), 145 (51%), 117 (58%), 102 (65%).

2b: $R_f=0.67$ (1:1 ethyl acetate/hexane): ¹H NMR (CDCl₃, 300 MHz) δ 8.97 (dd, 1H, $J=4.2, 1.8$ Hz, Ar-H), 8.54 (dd, 1H, $J=8.4, 1.5$ Hz, Ar-H), 7.43 (dd, 1H, $J=8.4, 4.2$ Hz, Ar-H), 6.97 (s, 1H, Ar-H), 4.10 (s, 3H, OCH₃), 3.99 (s, 3H, OCH₃); MS (m/z), 269 (M^+ , 54%), 267 (M^+ , 55%), 252 (100%), 158 (79%), 102 (55%).

RESULTS AND DISCUSSION

Dimethoxyquinoline (**1**) was submitted to reaction with NBS (2 equivalent) at room temperature for 2 h in different solvents. The results are collected in Table 1. When a solvent chosen from CCl₄, CH₂Cl₂ and CH₃CN was used, a mixture of regioisomers (**2a** and **2b**) was formed without notable selectivity. The apparently lower reactivity in case of CCl₄ may be a consequence of low solubility of NBS in CCl₄. Surprisingly, the substantial increase in the regioselectivity (6:1) for C(7) over C(6) and moderate isolation yields (79%) of **2b** was observed using THF as a solvent under otherwise identical conditions. In this case, the minimum amount of NBS relative to the substrate was found to be 2 equiv., and neither di-bromo nor *p*-quinone products were formed significantly. Moreover, in terms of reaction times, the bromination was slower in THF than in either CH₂Cl₂ or CH₃CN.

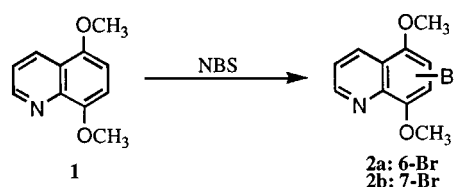


Table 1. Bromination of 5,8-Dimethoxyquinoline (**1**)^a

Solvent and catalyst system	Product yield (%) ^b		Selectivity (2a/2b) ^c
	2a	2b	
CCl ₄	5	6	1/1.2
CH ₂ Cl ₂	41	54	1/1.3
CH ₃ CN	56	38	1.5/1
THF	13	79	1/6.1
THF K ₂ CO ₃ (1eq.)	-	-	-
THF K ₂ CO ₃ (0.5eq.) ^d	8	81	1/10.1
THF H ₂ SO ₄ (cat.) ^e	28	66	1/2.4

^aStandard conditions: 2 equiv. NBS at 25 °C for 2 h. ^bIsolated yields. ^cRatios of **2a/2b** were of isolated products. ^d2 equiv. NBS at refluxing temp. for 6 h.

High regioselectivity observed in the NBS/THF-bromination, coupled with the fact that at least 2 equiv. of NBS are required to complete the relatively slow bromination, lead us to believe that the mechanism of the reaction involves initial formation of N(1)-bromo-5,8-dimethoxyquinolinium ion intermediate, stabilized in solvating medium, THF. Although the quaternary nitrogen deactivates the dimethoxy benzene ring towards electrophilic attack, the presence of the two methoxy groups might override this effect. Consequently, the bromination at the *meta* position (C-7) of the deactivating group is preferred with respect to the *para* position (C-6).

Therefore, an attempt was made to promote the N(1)-bromination before the ring bromination by addition of anhydrous potassium carbonate to NBS/THF. The results obtained with the catalyst systems are also collected in Table 1. As expected, the inorganic base facilitated formation of the quinolinium ion salts and increased the regioselectivity up to 10.1:1 in favor of C(7)-bromination. The previously reported⁸ bromination procedure for 5-nitro-8-hydroxyquinoline (NBS/THF-cat.H₂SO₄) was also employed with modification, but a decrease in regioselectivity was observed. Moreover, we checked that **2b** could be easily converted to the corresponding 7-bromoquinoline-5,8-dione by mild oxidative demethylation using cerium (IV) ammonium nitrate.⁹

In summary, data reported in this communication show that the regioselective bromination of 5,8-dimethoxyquinoline **1** at C(7) position can be easily achieved, thus providing a new pathway to 7-bromoquinoline-5,8-dione. Further studies on the utility of the N(1) atom of **1** as control element directing the regiochemistry of the bromination are currently underway.

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