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Tetrahedron
Tetrahedron 60 (2004) 4945–4951

Simple preparation of 7-alkylamino-2-methylquinoline-5,8-diones: regiochemistry in nucleophilic substitution reactions of the 6- or 7-bromo-2-methylquinoline-5,8-dione with amines☆,☆☆

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Received 16 February 2004; revised 16 April 2004; accepted 16 April 2004

Abstract—7-Alkylamino-2-methylquinoline-5,8-diones (**7**) were prepared from 6-bromo-2-methylquinoline-5,8-dione (**2**) not from 7-bromo-2-methylquinoline-5,8-dione (**1**). The chemistry of the transformation of 6-bromo-2-methylquinoline-5,8-dione (**2**) and various alkylamines, such as piperidine, 2-methylaziridine, benzylamine, *n*-butylamine, cyclohexylamine, *t*-butylamine, and ammonia, to 7-alkylamino compounds **7** as well as the transformation of 7-bromo compound **1** and the alkylamines to 6-alkylamino-2-methylquinoline-5,8-diones **11** was studied. The efficient and simple synthetic routes of the key intermediates, 6- and 7-bromo-2-methylquinoline-5,8-diones (**2** and **1**), from 5,8-dihydroxy-2-methylquinoline (**15**) and 5,7-dibromo-8-hydroxy-2-methylquinoline (**9**), respectively, were developed. We also proposed the mechanism for the unusual regioselectivity on the nucleophilic amination of 6- and 7-bromo-2-methylquinoline-5,8-diones (**2** and **1**).
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1. Introduction

Quinoline- and isoquinoline-5,8-diones have wide spectra of biological activities as antitumor, antibacterial, antifungal, antimalarial agents.[1–10] The syntheses and the biological activities of 6,7-functionalized quinoline-5,8-diones such as amino, hydroxyl, methoxy, thiol, and halogen have been reported.[1–4,11–17] As 7-amino group is the most critical segment in determining the antitumor activity of *Streptonigrin*, *Steptonigrone*, and *Lavendamycin*,[18] 7-amino-2-methylquinoline-5,8-dione (**7g**) has been the focus of synthetic efforts. Recently, Behforouz reported a short and efficient synthetic method of 7-amino-2-methylquinoline-5,8-dione (**7g**) as well as *Lavendamycin* from 7-acetylamino-2-methylquinoline-5,8-dione and β-methyltryptophan.[19,20] But to our knowledge, there has been no report on the syntheses of 7-alkylamino-2-methylquinoline-5,8-diones **7** as major products except our previous report[10] due to their synthetic problems such as preferential C6 substitution or addition of nucleophiles,[1,11,13,21] while 7-amino or 7-acetylaminoquinoline-5,8-diones were prepared from the reduction of azide and nitro substituents.[19,20] Recently, we published a report, in which, 7-alkylamino-2-methylquinoline-5,8-diones **7** were synthesized by the new synthetic route—nucleophilic substitution of amines and debromination—from 6,7-dibromo-2-methylquinoline-5,8-dione (**3**).[10] But this method has two drawbacks. First, as there is a regioselectivity between C6 and C7 in amination of 6,7-dibro-2-methylquinoline-5,8-dione (**3**), we could obtain the C7 aminated product only as moderate yields (50–60%) in optimized aprotic solvent such as dioxane. Second, in debromination step, we could not prepare some kinds of alkylamino compounds such as 2-methylaziridine, benzylamine and *t*-butylamine which are unstable in acidic condition because of the prevalently ongoing dealkylation. Thus we tried to discover another synthetic route for the preparation of the 7-alkylamino-2-methylquinoline-5,8-diones **7** including the alkylamino groups which are unstable in acidic conditions.

Herein, we wish to report the preparation of various 7-alkylamino-2-methylquinoline-5,8-diones **7** by a new efficient route. It is noteworthy that the conventional alkylation reactions on 7-amino group do not proceed due to its lack of nucleophilicity. The C2 methyl group could be

☆ CDRI Communication No. 6414.

☆☆ Supplementary data associated with this article can be found, in the online version at doi: 10.1016/j.tet.2004.04.041

Keywords: Quinoline-5,8-dione; 7-Amino-2-methylquinoline-5,8-dione; Nucleophilic substitution reactions; Regiochemistry; Alkylamination.

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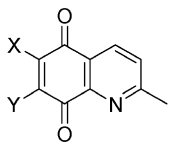
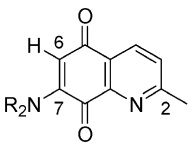
doi:10.1016/j.tet.2004.04.041

used for coupling with CD ring of *Lavendamycin* by reported method.[19,20]



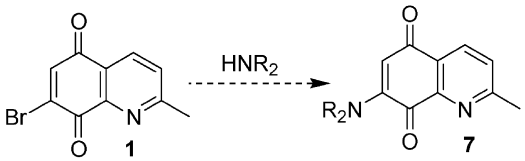
1, X = H, Y = Br,
2, X = Br, Y = H,
3, X = Y = Br,
4, X = Y = H,
5, X = OCH_3, Y = H,
6, X = H, Y = OCH_3



7a, R_2N = piperidinyl,
7b, R_2N = 2-methylaziridinyl,
7c, R_2N = benzylamino,
7d, R_2N = *n*-butylamino,
7e, R_2N = cyclohexylamino,
7f, R_2N = *t*-butylamino,
7g, R_2N = amino

2. Results and discussion

There were many reports on the preparation of 7-amino-quinoline-5,8-dione (**7g**) by nucleophilic azide substitution of 7-bromoquinoline-5,8-dione (**1**) followed by reduction to the amino group[22,23] and 6-aminoquinoline-5,8-dione (**12g**) by direct amine substitution of 6-methoxyquinoline-5,8-dione[21] and we also detected that 7-methoxyquinoline-5,8-dione yields 7-alkylamino-2-methylquinoline-5,8-dione **7** by nucleophilic amine substitution in low yields.[10] Thus to find an efficient synthetic route for the preparation of 7-alkylamino compounds **7**, we have designed a direct amination reaction of 7-bromoquinoline-5,8-dione (**1**) as shown in Scheme 1.

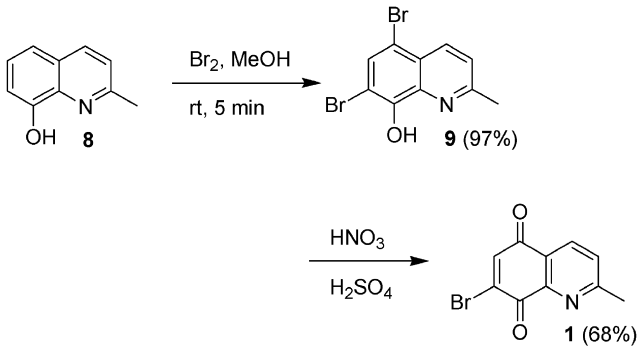


Scheme 1. A proposed new synthetic route for 7-alkylamino-2-methyl-quinoline-5,8-diones.

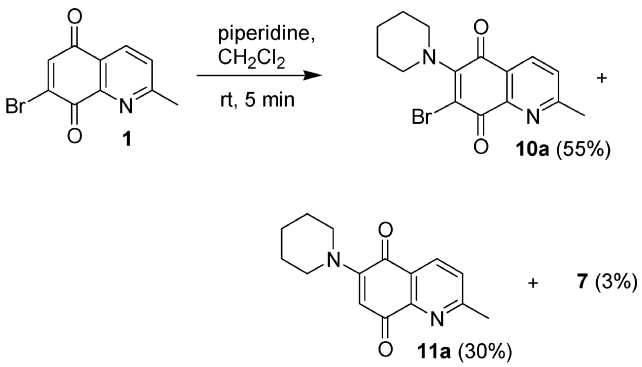
2.1. The preparation of 7-bromoquinoline-5,8-dione (1)

Petrow and Sturgeon reported a synthetic route for the preparation of **1** from 8-hydroxy-5-nitroso-2-methylquinoline by oxidation of nitroso to nitro group, selective bromination on the C7 position, reduction of nitro to the amino group, and oxidation to 7-bromo-2-methylquinoline-5,8-dione (**1**).[24] This procedure contained five steps and produced **1** in low yields. We have tried to discover an efficient and easy synthetic route for 7-bromo-2-methyl-quinoline-5,8-dione (**1**). Various synthetic routes were examined to synthesize 7-bromo compound **1**. Among them, **1** was prepared from very simple starting material, 8-hydroxy-2-methylquinoline (**8**) in two steps with 66% yield as shown in Scheme 2. Simple bromination of **8** gave 5,7-dibromo-8-hydroxy-2-methylquinoline (**9**) in 97% yield at rt for 5 min. The oxidation using 61% of nitric acid in the presence of concentrated sulfuric acid provided **1** in 68% yield.

Surprisingly, direct nucleophilic amination of 7-bromo compound **1** using piperidine gave predominantly the 6-piperidyl compounds **10a** (55%), **11a** (30%), and the

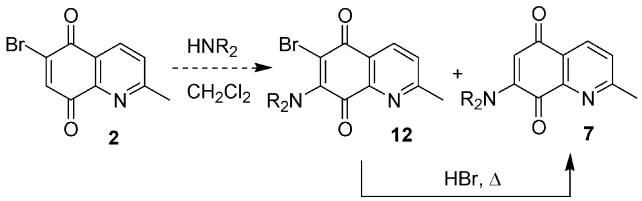


Scheme 2.



Scheme 3. The direct amination of 7-bromo-2-methylquinoline-5,8-dione (**1**).

desired 7-piperidyl compound **7a** in a low yield (3%) as shown in Scheme 3. At this point, the regiochemistry of C6 and C7 positions were thoroughly investigated. Therefore, it was expected the direct nucleophilic amination of 6-bromo-2-methylquinoline-5,8-dione (**2**) would produce 7-amino compounds **12** and **7** (Scheme 4). The debromination reactions of 6-bromo-7-alkylamino compounds **12** to **7** were developed by our group.[10]

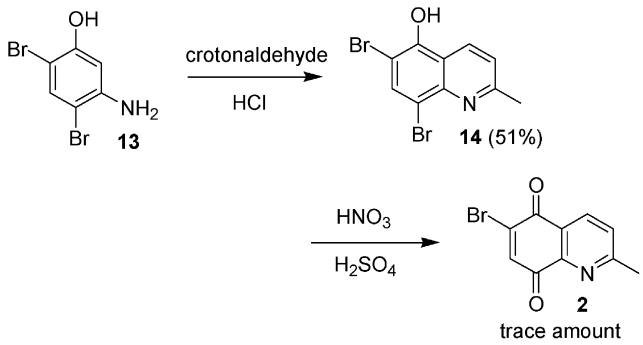


Scheme 4. Another proposed new synthetic route for 7-alkylamino-2-methylquinoline-5,8-diones.

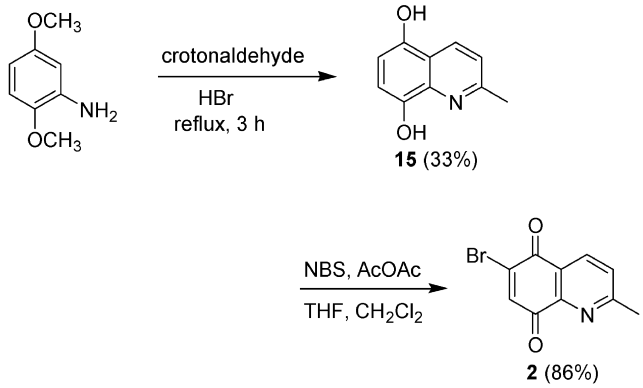
2.2. The preparation of 6-bromoquinoline-5,8-dione (2)

As prepared **1**, we expected that the direct oxidation by nitric acid of 6,8-dibromo-5-hydroxy-2-methylquinoline (**14**) would give **2** (Scheme 5). Unfortunately, we could obtain **2** in a trace amount. The difference of the electron donating abilities between 5-hydroxy and 8-hydroxy groups showed the different reactivities. Generally, it is known that the electron rich aromatic compounds are more easily oxidized. The 8-hydroxy group is thought to have more powerful electron donating ability by the formation of an intramolecular hydrogen bond with N1 nitrogen.

As shown in Scheme 6, we could prepare **2** from



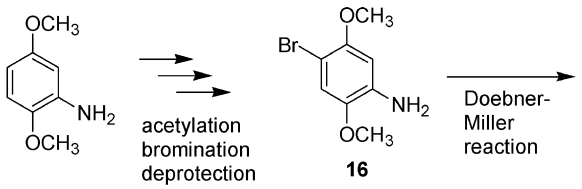
Scheme 5. Oxidation of 6,8-dibromo-5-hydroxy-2-methylquinoline.

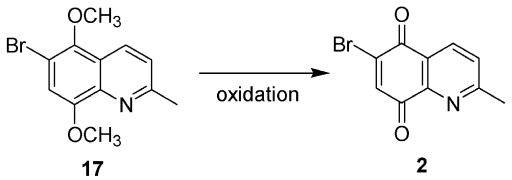


Scheme 6.

2,5-dimethoxyaniline in a reasonable yield by Doebner–Miller reaction[25] followed by oxidation using NBS. The regiochemistry of 6-bromo-2-methylquinoline-5,8-dione synthesized was identified by comparison with the authentic compound prepared by the route as shown in Scheme 7. Using this chemistry only the mono bromo compound **17**, 6-bromo-5,8-dimethoxy-2-methylquinoline was obtained which was oxidized via our recently reported method[26] using NBS with catalytic sulfuric acid and water.

Table 1 shows the results of the various 7-alkylamino compounds **7** prepared by direct nucleophilic aminations from 6-bromo-2-methylquinoline-5,8-dione (**2**). The reaction in the aprotic solvents such as dichloromethane gave the maximum yield of **7**. The addition of triethylamine





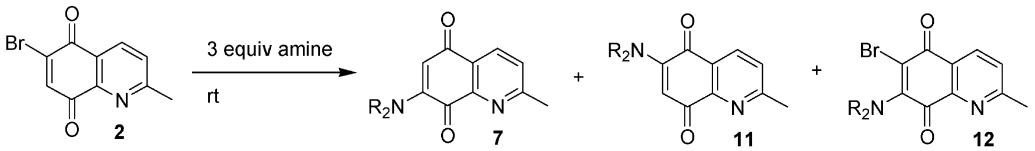
Scheme 7.

increased the selectivity of 7-amino products by trapping the generated HBr that can form the salt with N1 nitrogen. We could also obtain the 6-alkylamino compounds **11** from 6-bromo compound **2** with 40–60% yields by addition of Lewis acid in polar protic solvent as shown in Scheme 8.[28]

2.3. Plausible mechanism for the selective oxidative bromination of 5,8-dihydroxy-2-methylquinoline to 6-bromo-2-methylquinoline-5,8-dione

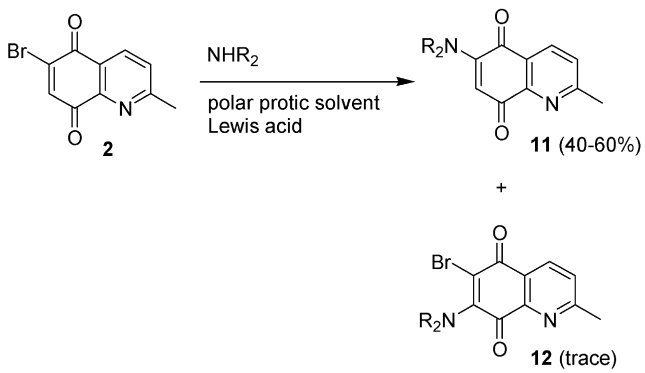
According to Scheme 6, 6-bromo-2-methylquinoline-5,8-dione (**2**) could efficiently and easily be obtained from 5,8-dihydroxy-2-methylquinoline (**15**) in gram-reaction scale. Scheme 9 shows the plausible mechanism for the selective oxidative bromination of **15** to **2**. This mechanism consists

Table 1. Amination of 6-bromo-2-methylquinoline-5,8-dione[a]



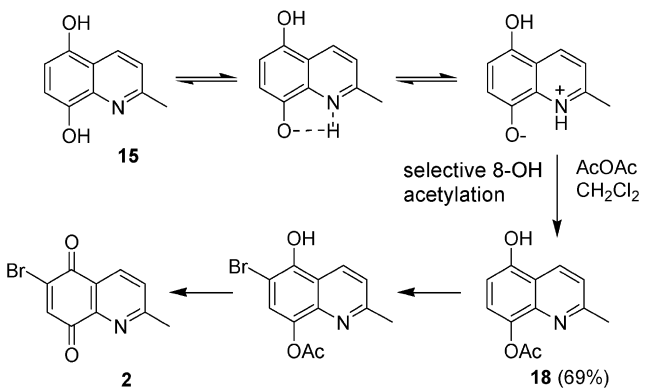
Solvent (25 mL)	Amine (3 equiv.)	Et_3N (mL)	Time (min)	**7** (%)	**11** (%)	**12** (%)	Total yield (%)
MeOH	Piperidine	—	10	**7a** (35)	**11a** (44)	**12a** (trace)	79
Dioxane	Piperidine	—	10	**7a** (70)	**11a** (7)	**12a** (trace)	77
Benzene	Piperidine	—	10	**7a** (75)	**11a** (18)	**12a** (trace)	93
CH_2Cl_2	Piperidine	—	10	**7a** (88)	**11a** (10)	—	98
CH_2Cl_2	2-Methylaziridine	—	15	**7b** (88)	**11b** (11)	—	99
CH_2Cl_2	2-Methylaziridine	0.5	15	**7b** (94)	**11b** (5)	—	99
CH_2Cl_2	Benzylamine	—	10	**7c** (55)	**11c** (5)	**12c** (16)	76
CH_2Cl_2	Benzylamine	0.5	10	**7c** (87)	**11c** (2)	**12c** (3)	92
CH_2Cl_2	*n*-Butylamine	—	10	**7d** (55)	—	**12d** (25)	80
CH_2Cl_2	*n*-Butylamine	0.5	10	**7d** (93)	—	**12d** (6)	99
CH_2Cl_2	Cyclohexylamine	0.5	30	**7e** (74)	—	**12e** (8)	82
CH_2Cl_2	*t*-Butylamine[b]	0.5	48 h	**7f** (48)	—	**12f** (4)	52
CH_2Cl_2	NH_4OH (1.5 mL)	1.5	90	**7g** (34)	—	**12g** (13)	47

[a] See general procedure in Section 4.
[b] 6 equiv. of amine was used.



Scheme 8.

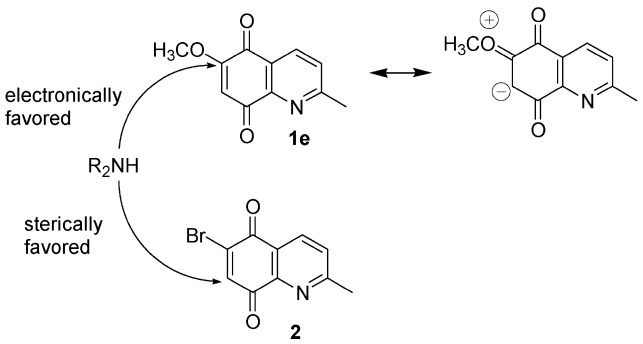
of three steps: (1) selective acetylation of 8-hydroxy group of **15** without base, (2) bromination using NBS onto the C6 position, and (3) oxidation using another equiv of NBS. Therefore, we added 2 equiv. of NBS because it is used as a brominating agent as well as oxidant. The key-intermediate, 5,8-dihydroxy-2-methylquinoline (**15**) could be prepared from 2,5-dimethoxyaniline via Doebner–Miller reaction and demethylation using concentrated HBr in 50–60% yield.[27]



Scheme 9.

When the base such as triethylamine was added, compound **15** was diacetylated on both 5- and 8-hydroxy and this diacetylated compound was not oxidized at the NBS condition. In addition, the direct treatment of NBS in methanol to 5,8-dihydroxy-2-methylquinoline (**15**) provided 2-methylquinoline-5,8-dione (**4**) in a 77% yield. On the inverse regioselectivity of nucleophilic amination of **1** and **2**, some papers reported the prevalent attack on the C6 position[1] is due to the chelation of metal cation between 8-oxygen and 1-nitrogen, and it is generally accepted that chelating effect is important for regioselectivity.[13,28] Actually, we experienced the chelating effect and hydrogen bonding effect in Table 1 (entry 1) and Scheme 8. We also detected that the nucleophilic aminations of 7-bromo-2-methylquinoline-5,8-dione (**1**) yielded the 6-amino compounds **10** and **11**. On the other hand, the neucleophilic aminations of 6-bromo-2-methylquinoline-5,8-dione (**2**) yielded the 7-amino compounds **7** and **12** as major products in non-polar aprotic solvents. It was reported that the 6-methoxy and 7-methoxy compounds each produced 6-amino and 7-amino compounds on the amine substitution of the 6- or 7-methoxy-2-methylquinoline-5,8-dione.[21] From those results, we could conclude that the chelating and intramolecular hydrogen bonding effect in polar protic solvent is important on the regioselectivity, while in non-polar aprotic solvent, the regiochemistry is mainly determined by properties of substituents on C6 or C7 position.

We propose the regioselectivity on the basis of electronic and steric effects. As shown in Scheme 10, the electron donating ability of methoxy group increases the electron density at the C7 position in place of *ortho*-position, consequently making the nucleophilic attack on the *ipso*-position favorable. On the other hand, when the bromine used as a leaving group, the bulkiness of bromine makes the *ipso*-attack difficult, thus it makes the attack at the C7 position in place of *ortho*-position favorable.



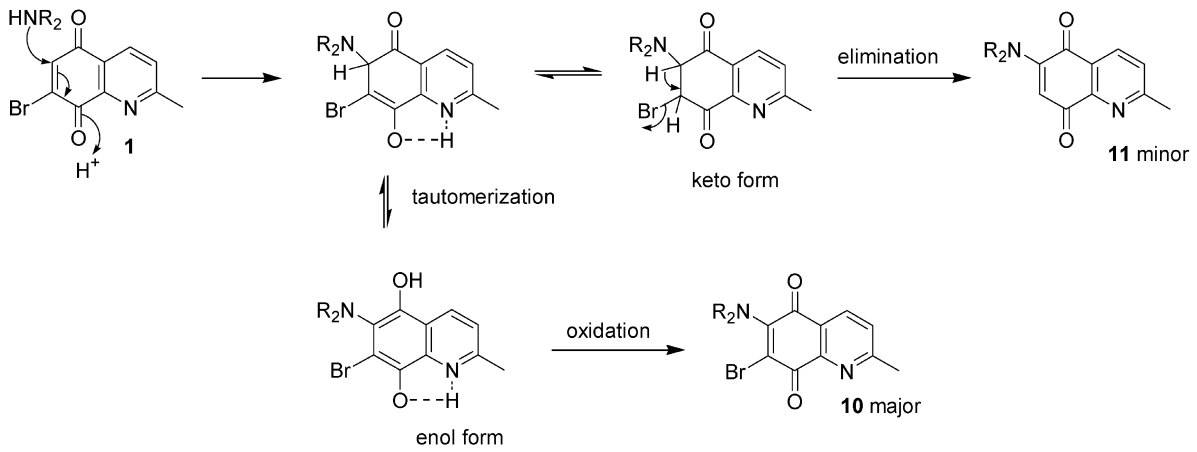
Scheme 10. Regioselectivity by substituent.

Furthermore, we obtained a different result between the 6-bromo (**2**) and 7-bromo-2-methylquinoline-5,8-dione (**1**) on the nucleophilic amination. The 7-bromo-2-methylquinoline-5,8-dione (**1**) yielded the 6-alkylamino-7-bromo-2-methylquinoline-5,8-diones **10** as major products, while 6-bromo-2-methylquinoline-5,8-dione (**2**) produced 7-alkylamino-2-methylquinoline-5,8-diones **7** as major products. We proposed that the different results are due to the intramolecular hydrogen bonding between the OH at the C8 and N1 as shown in Schemes 11 and 12.

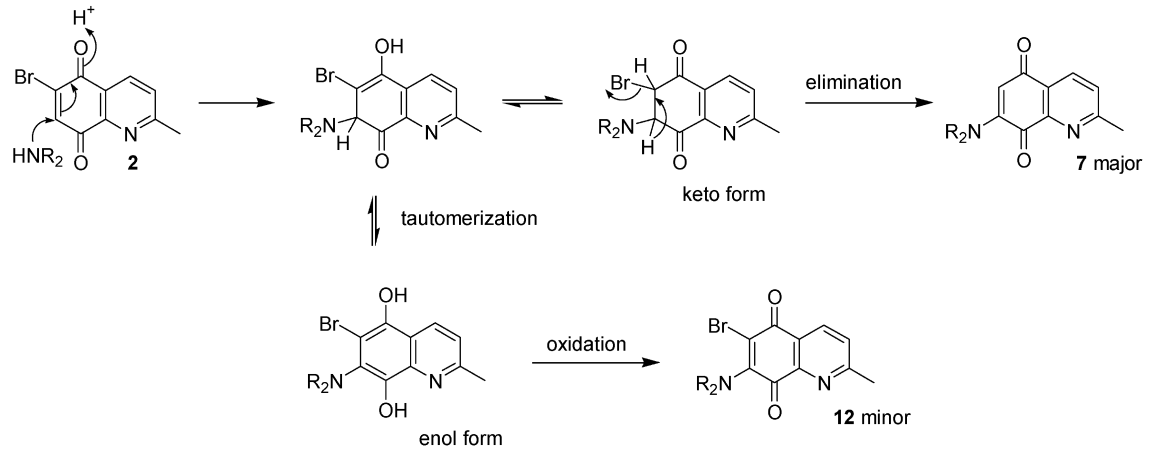
Scheme 11 shows that the intermediate can be in both in keto and enol forms, but the enol form will be more stable due to the intramolecular hydrogen bonding. As a result, following oxidation reaction of enol form provided 6-alkylamino-7-bromo-2-methylquinoline-5,8-dione **10** as a major product. But in case of 6-bromo-2-methylquinoline-5,8-dione (**2**), because there is no possibility for the more stabilizing the enol form, the 7-alkylamino-2-methylquinoline-5,8-diones **7** was obtained as a major product as shown in Scheme 12.

3. Conclusion

Recently, we reported a synthetic method for the preparation of various 7-alkylamino-2-methylquinoline-5,8-diones by nucleophilic amination of 6,7-dibromo-2-methylquinoline-5,8-dione followed by debromination upon treatment with hydrobromic acid.[10] As this synthetic route has some drawbacks, we developed the new synthetic route



Scheme 11. Proposed mechanism on the 6-alkylamino-2-methylquinoline-5,8-diones from 7-bromo-2-methylquinoline-5,8-diones.



Scheme 12. Proposed mechanism of 7-alkylamino-2-methylquinoline-5,8-diones from 6-bromo-2-methylquinoline-5,8-diones.

for 7-alkylamino-2-methylquinoline-5,8-diones by nucleophilic amination from 6-bromo-2-methylquinoline-5,8-dione, not from 7-bromo compound. Using this new method, we could prepare the alkylamino-2-methylquinoline-5,8-diones that could not be prepared by debromination method. During the research for the preparation of 7-alkylamino-2-methylquinoline-5,8-dione, we also discovered a new and efficient synthetic routes for the key intermediates, 6-bromo or 7-bromo-2-methylquinoline-5,8-diones.

4. Experimental

4.1. 5,7-Dibromo-8-hydroxy-2-methylquinoline (9)[29]

Bromine (10 mL) dissolved in MeOH (100 mL) was added into the mixture of 8-hydroxy-2-methylquinoline (**8**, 10.0 g, 62.8 mmol), $NaHCO_3$ (10 g) and MeOH (100 mL). After stirring for 5 min at rt, Na_2SO_3 (5 g) was added and then the mixture was filtered and washed with H_2O (200 mL) and was dried in vacuo to give **9** (19.34 g, 61.0 mmol, 97%) as a white solid.

4.1.1. 7-Bromo-2-methylquinoline-5,8-dione (1).[19] 5,7-Dibromo-8-hydroxy-2-methylquinoline (**9**, 10.8 g, 34.1 mmol) was dissolved in concentrated H_2SO_4 (40 mL), and HNO_3 (61%, 5 mL) was added for 30 min in the ice bath. And ice water (300 mL) was added and extracted with dichloromethane without neutralization and dried by Na_2SO_4 and was concentrated in vacuo to give **1** (5.81 g, 23.1 mmol, 68%) as a yellowish-white solid: ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.30 (d, J=8.2 Hz, 1H), 7.57 (d, J=8.2 Hz, 1H), 7.56 (s, 1H), 2.80 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$ +DMSO-d_6) δ 181.4, 175.9, 164.8, 145.3, 139.4, 139.1, 134.8, 128.1, 126.4, 23.7; MS (EI) 253 (M^+), 251 (M^+, 100), 225, 223, 197, 195, 172, 144, 116, 89, 74, 63, 53, 39. Anal. Calcd for $C_{10}H_6BrNO_2$: C, 47.65; H, 2.40; N, 5.56. Found: C, 47.26; H, 2.52; N, 5.51.

4.2. General procedure for amination of 7-bromo-2-methylquinoline-5,8-dione (1)

4.2.1. 7-Bromo-2-methyl-6-(piperidin-1-yl)quinoline-5,8-dione (10a).[10] 7-Bromo-2-methylquinoline-5,8-dione (**1**, 700 mg, 2.78 mmol) was dissolved in dichloromethane (20 mL) and piperidine (0.7 mL) was added. After stirring for 1 min at rt, H_2O (50 mL) was added into the mixture and extracted with dichloromethane, dried by Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography (40% EtOAc/hexane) to give **10a** (519 mg, 1.55 mmol, 55%), 2-methyl-6-(piperidin-1-yl)-quinoline-5,8-dione (**11a**, 215 mg, 0.84 mmol, 30%),

2-methyl-7-(piperidin-1-yl)quinoline-5,8-dione (**7a**, 22 mg, 0.08 mmol, 3%). See the analytical data in Ref. 10.

4.2.2. 2,4-Dibromo-5-aminophenol (13).[30] The title compound was prepared by acetylation of 3-aminophenol, followed by selective 2,4-dibromination and deacetylation.

4.2.3. 6,8-Dibromo-5-hydroxy-2-methylquinoline (14).[30] Crotonaldehyde (1.5 mL) was added into the mixture of 2,4-dibromo-5-aminophenol (**13**, 1.15 g, 4.31 mmol) and concentrated HCl (10 mL) and AcOH (10 mL), then the reaction mixture was refluxed for 30 min. The reaction mixture was neutralized by $NaHCO_3$ and extracted by EtOAc and was concentrated in vacuo. The residue was purified by flash column chromatography (60% EtOAc/hexane) to give **14** (691 mg, 2.18 mmol, 51%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.07 (bs, 1H), 8.23 (d, J=8.4 Hz, 1H), 7.74 (s, 1H), 7.05 (d, J=8.8 Hz, 1H), 2.49 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$ +DMSO-d_6) δ 159.7, 149.0, 143.7, 134.3, 131.1, 121.5, 119.6, 113.1, 102.9, 24.8; MS (EI) 319 (M^+), 317 (M^+), 315 (M^+), 156, 128, 101, 64, 51, 32 (100). HRMS (EI^+) m/z Calcd for $C_{10}H_7Br_2NO$ (M^+) 316.8874, found 316.8894.

4.2.4. 5,8-Dihydroxy-2-methylquinoline (15).[27] Crotonaldehyde (11.84 g, 169 mmol, 1.3 equiv.) was added into the mixture of 2,5-dimethoxyaniline (20 g, 130 mmol) and concentrated HBr (150 mL), then the reaction mixture was refluxed for 24 h and the reaction mixture was neutralized by $NaHCO_3$ and extracted by EtOAc and was concentrated in vacuo. The residue was purified by flash column chromatography (40% EtOAc/hexane) to give **15** (7.4 g, 42.3 mmol, 33%): ^{1}H NMR (200 MHz, $CDCl_3$ +DMSO-d_6) δ 8.41 (d, J=8.4 Hz, 1H), 7.26 (d, J=8.4 Hz, 1H), 6.93 (d, J=8.2 Hz, 1H), 6.77 (d, J=8.4 Hz, 1H), 2.70 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$ +DMSO-d_6) δ 156.6, 144.8, 144.1, 137.4, 131.3, 120.8, 118.0, 108.9, 107.9, 24.6; MS (EI) 175 (M^+, 100), 146, 118, 87, 74, 52, 39. HRMS m/z (EI^+) 175.0635, Calcd for $C_{10}H_9NO_2$ 175.0633.

4.2.5. 6-Bromo-2-methylquinoline-5,8-dione (2).[26] Acetic anhydride (2 mL) was added into the mixture of 5,8-dihydroxy-2-methylquinoline (**15**, 1.0 g, 5.57 mmol) and dichloromethane (40 mL) and THF (10 mL). After stirring at rt for 5 min, NBS (1.7 g, 9.55 mmol, 1.68 equiv.) was added and was stirred for 10 min and then H_2O (200 mL) including $NaHCO_3$ (3 g) added and extracted by dichloromethane and was concentrated in vacuo. The residue was purified by flash column chromatography (60% EtOAc/hexane) to give **2** (1.23 g, 4.89 mmol, 85.7%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.39 (d, J=8.4 Hz, 1H), 7.65 (s, 1H), 7.59 (d, J=8.0 Hz, 1H), 2.80 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$ +DMSO-d_6) δ 178.6, 175.1, 163.3, 144.3, 137.8, 137.0, 133.3, 125.4, 123.7, 22.9.; MS (EI) 253 (M^+, 100), 251 (M^+), 225, 223, 197, 195, 144, 116, 89, 63, 53, 39. Anal. Calcd for $C_{10}H_6BrNO_2$: C, 47.65; H, 2.40; N, 5.56. Found: C, 47.40; H, 2.55; N, 5.53.

4.3. General procedure for amination of 6-bromo-2-methylquinoline-5,8-dione (2) at Table 1

4.3.1. 2-Methyl-7-(2-methylaziridin-1-yl)quinoline-5,8-dione (7b).[10] 6-Bromo-2-methylquinoline-5,8-dione (**2**, 200 mg, 0.79 mmol) was dissolved in dichloromethane (10 mL) and triethylamine (0.5 mL) then 2-methylaziridine (0.19 mL) was added at rt. After stirring for 5 min, H_2O (100 mL) was added and was extracted with dichloromethane and dried by Na_2SO_4 and was concentrated in vacuo. The residue was purified by flash column chromatography (40% EtOAc/hexane) to give **7b** (170 mg, 0.75 mmol, 94%) as a yellow solid: See detail data are in Ref. 10. 2-Methyl-6-(2-methylaziridin-1-yl)quinoline-5,8-dione (**11b**, 8 mg, 0.04 mmol, 5%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J=8.0 Hz, 1H), 7.49 (d, J=8.0 Hz, 1H), 6.39 (s, 1H), 2.77 (s, 1H), 2.40–2.43 (m, 1H), 2.20–2.23 (m, 2H), 1.47 (d, J=6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.2, 181.3, 164.9, 157.1, 147.5, 134.5, 126.8, 126.3, 118.9, 36.3, 34.5, 25.2, 17.5; MS (ESI, positive) 229 (M^++1, 100). HRMS (EI^+) m/z Calcd for $C_{13}H_{12}N_2O_2$ (M^+) 228.0899, found 228.0889.

4.3.2. 7-Benzylamino-2-methylquinoline-5,8-dione (7c). ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.29 (d, J=8.0 Hz, 1H), 7.50 (d, J=8.0 Hz, 1H), 7.28–7.40 (m, 5H), 6.42 (bs, 1H), 5.80 (s, 1H), 4.41 (d, J=6.0 Hz, 1H), 2.73 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 182.0, 180.4, 163.0, 147.9, 146.1, 135.6, 134.5, 129.0, 128.4, 128.2, 128.1, 127.6, 100.9, 46.9, 29.6, 24.9; MS (EI) 278 (M^+), 276, 261, 194, 174, 117, 91 (100), 77, 65, 51, 39. HRMS (EI^+) m/z Calcd for $C_{17}H_{14}N_2O_2$ (M^+) 278.1055, found 278.1059.

4.3.3. 6-Benzylamino-2-methylquinoline-5,8-dione (11c). ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.25 (d, J=8.0 Hz, 1H), 7.27–7.45 (m, 6H), 6.20 (bs, 1H), 5.95 (s, 1H), 4.39 (d, J=5.4 Hz, 1H), 2.77 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 181.5, 181.3, 165.4, 148.5, 147.0, 135.4, 134.1, 128.8, 128.0, 127.5, 126.0, 125.0, 102.2, 46.7, 26.3; MS (EI) 278 (M^+, 100), 261, 201, 187, 174, 117, 91, 77, 65. HRMS (EI^+) m/z Calcd for $C_{17}H_{14}N_2O_2$ (M^+) 278.1055, found 278.1056.

Compounds **12a**, **12c-g**, **7d-g**.[10] See detail data are in Ref. 10.

4.3.4. 8-Acetoxy-5-hydroxy-2-methylquinoline (18). Acetic anhydride (2.7 mL, 28.8 mmol, 0.9 equiv.) was added into the mixture of 5,8-dihydroxy-2-methylquinoline (**15**, 5.6 g, 32.0 mmol) and dichloromethane (50 mL). After stirring at rt for 30 min, the reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography (40% EtOAc/hexane) to give **18** (4.71 g, 22.0 mmol, 69%): ^{1}H NMR (200 MHz, $CDCl_3$ +DMSO-d_6) δ 9.96 (s, 1H), 8.37 (d, J=8.4 Hz, 1H), 7.19 (d, J=8.4 Hz, 1H), 7.10 (d, J=8.6 Hz, 1H), 6.74 (d, J=8.4 Hz, 1H), 2.61 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$ +DMSO-d_6) δ 167.9, 156.9, 149.3, 138.8, 136.8, 129.3, 119.1, 118.9, 116.9, 104.7, 23.3, 18.7; MS (CI) 218 (M^++1, 100), 204, 176. Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 65.98; H, 5.48; N, 6.28.

4.3.5. 6-Bromo-2-methylquinoline-5,8-dione (2) from 8-acetoxy-5-hydroxy-2-methylquinoline (18). NBS (5.47 g, 30.7 mmol, 2.47 equiv.) was added into the mixture of 8-acetoxy-5-hydroxy-2-methylquinoline (2.69 g, 12.4 mmol) and dichloromethane (70 mL). After stirring at rt for 30 min, the solvent was removed in vacuo. The

residue was purified by flash column chromatography (60% EtOAc/hexane) giving **2** (2.30 g, 9.0 mmol, 73%).

Acknowledgements

This work was supported by National Research Laboratory Program.

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