NEW EFFICIENT SYNTHESES OF 6,7-DIBROMOQUINOLINE-5,8-DIONES

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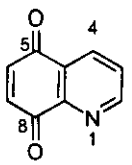
Abstract - Key intermediates for potential antitumor or antifungal agents, 2- and 3-methyl-6,7-dibromoquinoline-5,8-diones have been synthesized from 2,5-dimethoxyaniline and acrolein derivatives in three-step-one-pot with 38-41% isolation yields using Skraup reaction. The three steps are ring formation of quinoline, didemethylation, and oxidation of hydroquinone including dibromination on C6 and C7 positions.

Streptonigrin[1] and lavendamycin,[2] antitumor antibiotics isolated from *Streptomyces flocculus* and *lavendulae*, respectively, are highly substituted 5,8-quinolinediones (**1**). Due to their wide spectra of biological activities, variously substituted 5,8-quinolinediones were synthesized and tested their biological activities over several decades. The chemistry and structure-activity relationships of the C-6 and/or C-7-substituted quinoline-5,8-diones are the major concerns of previous reports.[3]



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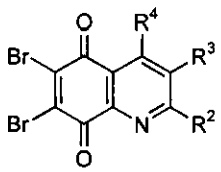


2a, $R^2 = R^3 = R^4 = H$
2b, $R^2 = CH_3$, $R^3 = R^4 = H$
2c, $R^2 = H$, $R^3 = CH_3$, $R^4 = H$
2d, $R^2 = R^3 = H$, $R^4 = CH_3$

Displacement reaction of 6- and 7-bromide of compound (**2a**) with nucleophile has been studied well.[4,5] The C6 and C7 substituents are mainly such as amino, alkoxy, thioalkoxy, and their derivatives, as well as alkyl, halogen and nitro groups. Thus, while the chemistry of **2a** being studied well, the chemistry of 2-methylquinoline-5,8-dione (quinaldine-5,8-dione), 3-methylquinoline-5,8-dione, and 4-methylquinoline-5,8-dione (lepidine-5,8-dione) has not been studied much. We report here more practical route to the key intermediate (**2b-d**) using Skraup reaction.

The reports of synthetic methods of quinoline-5,8-dione in the literature could be summarized by four major routes; 1) Skraup reaction,[5-8] 2) Friedlander reaction,[9] 3) Diels-Alder reaction,[10] 4) Oxidation from 8-hydroxyquinoline.[11] Nonetheless the starting anilines for Skraup reaction are easily available and not expensive in general, a few Skraup reactions have been applied for the syntheses of quinoline-5,8-diones because of their low yield. Due to the limitation of starting material in the Friedlander reaction and Diels-Alder reaction, the application of these reaction is not practical. Elslager *et al.* reported the syntheses and antimalarial activity of 6-substituted 5,8-dimethoxyquinaldines.[12] Wan *et al.* also reported new quinaldine-5,8-dione derivatives using Skraup reaction (20%), starting from 2-nitro-4-methoxyaniline and acrolein.[6] Lown and Sim also synthesized 2-(2-nitrophenyl)-5,8-dimethoxyquinoline using Skraup reaction (15%).[7] Recently, Kubo *et al.* reported the syntheses of 5,6,8- and 5,7,8-trimethoxyquinolines with improved yield (43-55%) from trimethoxyanilines, which are more electron rich anilines than dimethoxyaniline, and acrolein.[8]

Various Skraup reaction conditions were explored using the commercially available 2,5-dimethoxyaniline (**3**) and crotonaldehyde (**4b**), but the most reactions gave very low yields (Table 1, Scheme 1). The best result was obtained by using only conc. HBr (48%) at 70 °C for 15 min. On the basis of TLC analysis of the reaction mixture, most of **3** was disappeared at 15 min, however, cyclization was completed at 30 min, and in this time, monodemethylated product, 5-hydroxy-8-methoxyquinaldine, was also formed.

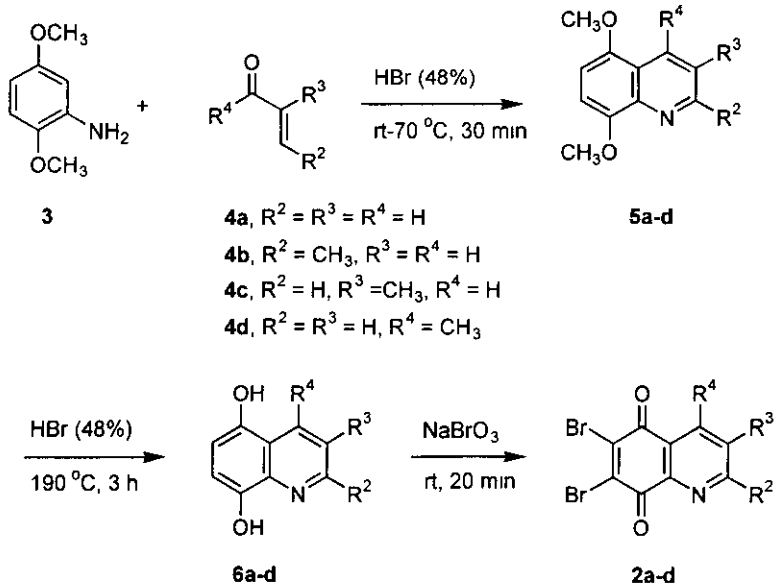
In order to synthesize key intermediates (**2**), we have performed the three reactions with pure isolated compounds according to Scheme 1. There were some difficulties to isolate polar compounds, especially, 5,8-dihydroxy derivatives (**6**). We have carried out these three-step reactions at one-pot without isolation and purification of **5** and **6**, and just with one purification of **2** by flash column chromatography, providing **2** in higher yield. This process contains three steps; 1) ring formation of quinoline with 2,5-dimethoxyaniline (**3**) and crotonaldehyde (**4b**) or methacrolein (**4c**) by Skraup reaction in the presence of conc. hydrogen bromide, 2)

didemethylation by just raising the reaction temperature, and 3) oxidation of hydroquinone by adding oxidant, $NaBrO_3$. During the last step, bromides are added to C6 and C7 positions by Michael addition. This three-step-one-pot reaction process provides compounds (**2b-c**) in the reasonable yields while **2a** and **2d** in much lower yields and the results of are: **2b**, 41%; **2c**, 38%, **2a**, 9%; **2d**, 6% (Ketone is less reactive on ring formation than aldehyde).

Table 1. Skraup Reactions of 2,5-Dimethoxyaniline (**3**) and Acrolein Derivatives (**4**).

entry	acroleins	acid	reaction condition	yield (%)
1	**4b**	HCl/dioxane	rt, 5 min	23
2		HCl/dioxane	0 - rt, 1 h	28
3		HCl/CH_2Cl_2	rt, 5 h	39
4		HBr/ CH_3OH	reflux, 1 h	0
5		$AlCl_3/CH_2Cl_2$	rt, 30 min	37
6		H_2SO_4	reflux, 10 min	0
7		HBr(48%)	70 °C, 15 min	52
8	**4c**	HBr(48%)	100 °C, 10 min	51
9	**4d**	HBr(48%)	100 °C, 2 h	11
10	**4a**	HBr(48%)	70 °C, 30 min	18

Scheme 1. Three-step-one-pot Reaction.



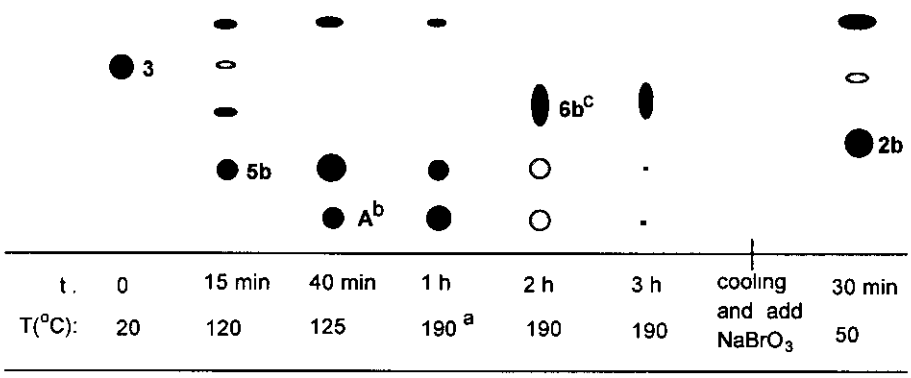
This three-step-one-pot syntheses of quinoline-5,8-diones would be useful as practical syntheses of other derivatives.

EXPERIMENTAL

Materials and Methods. Column chromatography was done by Flash chromatography with silica gel (EM Science, 230-400 mesh ASTM). Solvents and reagents were purchased from the following commercial sources: Aldrich, Kanto, Acros. Analytical thin layer chromatography (TLC) was performed with Merck silica gel F-254 glass-backed plates. Visualization was achieved by phosphomolybdic acid (PMA), $KMnO_4$, or anisaldehyde spray reagents, iodine, or UV illumination. ^1H and ^{13}C NMR spectra were obtained on Varial Gemini-200 spectrometers and are reported in parts per million downfield from internal tetramethylsilane. MS spectra were obtained on HP590 GC/MS 5972 MSD spectrometer.

General procedure of three-step-one-pot reaction for 2- and 3-methyl-6,7-dibromoquinoline-5,8-diones (2b, c): Crotonaldehyde (1.00 mL, 12.1 mmol) was added to the mixture of 2,5-dimethoxyaniline (1.00 g, 6.54 mmol) and conc. HBr (48%, 15 mL) in a two-neck flask (200 mL) with stirring at 20 °C. The mixture was heated at 190 °C for 3 h. The reaction mixture was cooled to rt and H_2O (15 mL) was added with stirring. $NaBrO_3$ (2.00 g, 13.25 mmol) was added slowly. After stirring for 15 min, the reaction mixture was neutralized with aqueous $NaHCO_3$ (10%) and extracted with EtOAc. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (40% EtOAc/hexane) to give 0.89 g (41%) of **2b**, as a brownish-yellow solid: mp 110 °C (decomp) (20% EtOAc/hexane); ^1H NMR (200 MHz, $CDCl_3$) δ 2.75 (s, 3H), 7.55 (d, J = 8.0 Hz, 1H), 8.33 (d, J = 8.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.6, 124.3, 126.6, 134.4, 140.1, 141.2, 144.4, 164.3, 172.7, 174.9; MS(EI) m/z (relative intensity) 333 (M^+, 92), 331 (M^+, 100), 329 (M^+, 37), 252 (62), 250 (50), 197 (35), 195 (37), 133 (27), 131 (29), 115 (79), 63 (37). Anal. Calcd for $C_{10}H_5NO_2Br_2$: C, 36.31; H, 1.52; N, 4.23. Found: C, 36.34; H, 1.76; N, 4.03. **2c**: mp 103 °C (decomp) (20% EtOAc/hexane); ^1H NMR (200 MHz, $CDCl_3$) δ 2.53 (s, 3H), 8.22-8.26 (m, 1H), 8.82-8.86 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.2, 126.0, 134.0, 138.0, 140.0, 141.6, 142.6, 154.3, 172.4, 174.2; MS(EI) m/z (relative intensity) 333 (M^+, 70), 331 (M^+, 95), 329 (M^+, 39), 252 (100), 250 (81), 196 (51), 194 (43), 133 (25), 131 (27), 115 (83), 63 (45). Anal. Calcd for $C_{10}H_5NO_2Br_2$: C, 36.31; H, 1.52; N, 4.23. Found: C, 36.53; H, 1.68; N, 4.00.

The TLC analyses of this three-step-one-pot reaction are as followed (silica gel, 40% EtOAc/hexanes):



[a]bath temperature, [b]A = 5-hydroxy-8-methoxyquinaldine, [c]Surprisingly, 5,8-dihydroxyquinaldine (**6b**) has a higher R_f value than **5b** and 5-hydroxy-8-methoxyquinaldine. Intra- or intermolecular hydrogen bonding between 8-hydroxy and nitrogen could decrease the polarity of the compound.

General procedure for 2- and 3-methyl-6,7-dimethoxyquinolines (5b, c): Crotonaldehyde (0.60 mL, 7.24 mmol) was added to the mixture of 2,5-dimethoxyaniline (1.00 g, 6.54 mmol) and conc. HBr (48%, 10 mL) in a two-neck flask (200 mL) with stirring at 20 °C. The mixture was heated at 70 °C for 15 min. The reaction was quenched by adding 50 mL of water at 70 °C and the reaction mixture was cooled down to rt. After extracting with EtOAc, the organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (40% EtOAc/hexane) to give 0.76 g (57%) of **5b**, as a yellow solid: mp 73.4-74.0 °C (hexane); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.71 (s, 3H), 3.83 (s, 3H), 3.94 (s, 3H), 6.58 (d, J = 8.6 Hz, 1H), 6.81 (d, J = 8.6 Hz, 1H), 7.21 (d, J = 8.6 Hz, 1H), 8.34 (d, J = 8.6 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.8, 53.9, 54.2, 101.1, 105.1, 118.1, 120.0, 129.3, 138.4, 147.1, 147.3, 156.9; MS(EI) m/z (relative intensity) 203 (M^+, 44), 188 (100), 173 (17), 160 (10), 145 (11), 130 (13), 77 (8). **5c**, as a light brown solid: mp 77.5-78.0 °C (hexane); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.27 (s, 3H), 3.68 (s, 3H), 3.81 (s, 3H), 6.43 (d, J = 8.4 Hz, 1H), 6.59 (d, J = 8.4 Hz, 1H), 8.05-8.09 (m, 1H), 8.59 (d, J = 2.2 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.9, 53.8, 54.1, 101.9, 104.0, 119.7, 127.8, 128.6, 137.0, 146.5, 147.8, 149.5; MS(EI) m/z (relative intensity) 203 (M^+, 60), 188 (100), 175 (15), 160 (15), 146 (6), 130 (12), 117 (16), 77 (10).

ACKNOWLEDGMENTS

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