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ISSN: 2278-1862

Journal of Applicable Chemistry

2019, 8 (6): 2343-2347

(International Peer Reviewed Journal)

Synthesis of Regioisomers of Barleria quinones-I and II

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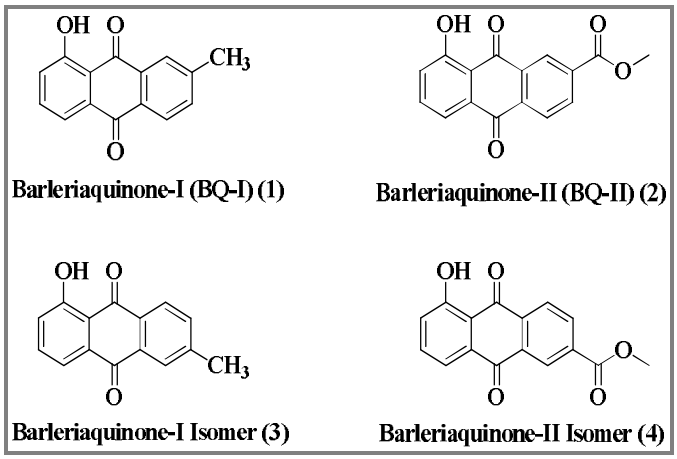
Accepted on 13th November, 2019

ABSTRACT

*Synthesis of regioisomers of barleriaquinone-I (**3**) and Barleria quinone-II (**4**) is accomplished byemploying simultaneous Heck and cross coupling reaction as the crucial step.*

Graphical Abstract



Structures of Barleriaquinone-I (BQ-I) (**1**); Barleriaquinone-II (BQ-II) (**2**) and their regioisomers.

Keywords: Heck and cross coupling reaction, Curtius reaction, Suzuki coupling, Regioisomers of Barleriaquinones-I and II

INTRODUCTION

Enormous number of naturally occurring quinones captivated the attention of synthetic chemists due to their structural distinctions and broad range of biological activities, such as anti-tumor, anti-cancer, antibacterial, antitrypanosomally, antineoplastic and anti-HIV activities [1]. Recently, Barleria

quinone-I (BQ-I) (**1**) and Barleriaquinone-II (BQ-II) (**2**) structurally related to anthracyclinones were isolated from *Barleria buxifolia* and tested for their cytotoxic activity [2]. The significance of anthraquinone derivatives have led to the development of numerous synthetic approaches [3].

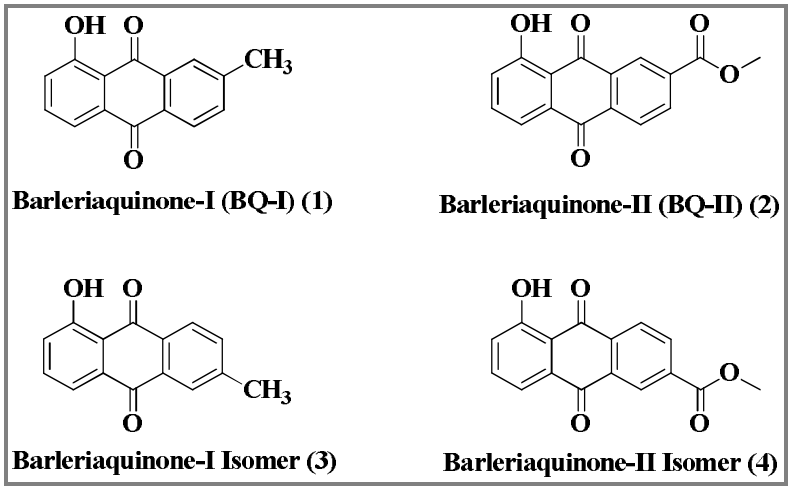


Figure 1. Structures of Barleriaquinone-I (BQ-I) (**1**); Barleriaquinone-II (BQ-II) (**2**) and their regioisomers.

Encouraged by the biological activity and our interest in the synthesis of natural products, we recently reported the synthesis of Barleriaquinone-I (BQ-I) (**1**) and Barleriaquinone-II (BQ-II) (**2**) [4]. Incontinuation of our endeavour to synthesize the regioisomers of Barleriaquinones, herein we wish to describe the synthesis of Barleriaquinone-I Isomer (**3**) and Barleriaquinone-II Isomer (**4**) utilizing Heck reaction as key step (Figure 1).

MATERIALS AND METHODS

General methods: Compounds **5**, **6a** and **6b** were synthesized according to the literature methods[4]. All reactions were performed in flame dried glassware under a nitrogen atmosphere using reagents and dry solvents as received from the suppliers. Reactions were monitored by normal phase thin-layer chromatography (TLC) using Merck's Silicagel 60 F-254 plates. All the intermediates and final compounds were purified by Bauchi's flash chromatography using Teledyne RediSep® normal-phase Silica flash columns as stationary phase. ^{1}H and ^{13}C NMR spectra were recorded on Agilent MR 400MHz and Bruker AVANCE NEO 400MHz (^{1}H NMR, 400 MHz; ^{13}C NMR, 100 MHz) instruments. $CDCl_3$ and DMSO-d_6 were used as solvents and tetramethylsilane as internal standard. Chemical shifts are reported in δ (ppm).Abbreviations for NMR data are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, brs = broad. NMR spectra were calibrated relative to their respective residual NMR solvent peaks, $CHCl_3$ =7.26 ppm (^{1}H NMR)/77.1 ppm (^{13}C NMR), DMSO = 2.50 ppm (^{1}H NMR)/39.5 ppm (^{13}C NMR). Mass spectra were obtained on a Water-Acquit UPLC system with PDA detector and TQD Mass detector or equivalent equipped with an electrospray ion source (ESI) operated in positive mode. All temperatures are reported in degrees centigrade. IR spectra were recorded on Perkin Elmer-spectrum 100 instrument between 4000 and 450 cm^{-1} under the operational conditions. Melting points were measured using Bauchi melting point apparatus. SFC purification was carried on SFC-PIC-002 system.

Synthesis of 5-hydroxy-9,10-dioxo-9,10-dihydroanthracene-2-carboxylic acid (7): To a solution of tert-butyl 5-hydroxy-9,10-dioxo-9,10-dihydroanthracene-2-carboxylate **(6b)** (1 g, 3.08 mmol, 1eq) in EtOH:THF:H_2O (1:1:1, 10 mL) were added LiOH.H_2O (648 mg, 15.43 mmol, 5eq) at room temperature. Resulting reaction mixture was stirred at 27°C for 48h. Reaction mixture was monitored by TLC [(TLC silica gel plate), mobile phase: 50% ethyl acetate in petroleum ether, 0.2 R_f, UV

active]). After completion of starting material, reaction mixture was evaporated under reduced pressure. Crude compound was quenched with aq. 4N citric acid solution (20 mL), filtered the obtained solid and dried to get 5-hydroxy-9,10-dioxo-9,10-dihydroanthracene-2-carboxylic acid **(7)** (800 mg, 96%) as yellow solid.IR (KBr Pellet)υ_{max}: 3429, 2923, 2853, 1742, 1683, 1642, 1598, 1573, 1448, 1417, 1304, 1276, 1182, 1150, 1119, 1068, 1035, 932, 896, 874, 836, 755, 709, 543; Melting Range: Charing at 300^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.29 (brs, 1H), 8.62 (d, *J* = 1.2 Hz, 1H), 8.40 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H), 8.32 (d, *J* = 8.0 Hz, 1H), 7.84 (t, *J* = 8.4 Hz, 1H), 7.75 (dd, *J* = 7.4 Hz, 0.8 Hz, 1H), 7.42 (dd, *J* = 8.0 Hz, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 187.5, 181.3, 165.9, 161.5, 137.3, 136.6, 135.3, 134.4, 133.2, 133.2, 127.3, 127.1, 124.2, 119.1, 116.1;ESI-MS: 267.10 (MH)-.

Synthesis of Barleriaquinone-II Isomer (4): To a solution of 5-hydroxy-9,10-dioxo-9,10-dihydroanthracene-2-carboxylic acid (**7**) (100 mg, 0.37 mmol) in MeOH (10 mL), con.H_2SO_4 (0.1 mL) was added under argon atmosphere at room temperature and the resulting reaction mixture was stirred at 75°C for 10 h. Reaction mixture was monitored by TLC [(TLC silica gel plate), mobile phase: 30% ethyl acetate in petroleum ether, 0.6 R_f, UV active]). After completion of starting material, reaction mixture was evaporated under reduced pressure to obtain crude compound which was purified by flash column chromatography by eluting with 10-20% ethyl acetate in petroleum ether and the compound fractions were concentrated under reduced pressure to give Barleriaquinone-II Isomer (**4**) (80 mg, 76%) as yellow solid. IR (KBr pellet)υ_{max}: 3429, 3090, 2956, 2924, 2852, 1728, 1667, 1641, 1605, 1594, 1577, 1457, 1371, 1346, 1311, 1264, 1243, 1220, 1180, 1162, 1115, 1092, 1065, 1036, 972, 897, 834, 793, 779, 746, 707, 550, 474; Melting Range: 168-172^{o}C; ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 12.50 (s, 1H), 8.93 (dd, *J* = 1.2 Hz, 0.4 Hz, 1H), 8.46 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H), 8.41 (dd, *J* = 8.0 Hz, 0.4 Hz, 1H), 7.89 (dd, *J* = 7.6 Hz, 1.2 Hz, 1H), 7.72 (t, *J* = 7.6 Hz, 1H), 7.36 (dd, *J* = 8.4 Hz, 1.2 Hz, 1H), 4.01 (s, 3H); ESI-MS: 283.17 (MH)+.

Synthesis of 6-Amino-1-hydroxyanthracene-9,10-dione (8): To a solution of 5-hydroxy-9,10-dioxo-9,10-dihydroanthracene-2-carboxylic acid (**7**) (250 mg, 0.93 mmol) in toluene (2 mL) were added Et_3N (0.403 mL, 2.79 mmol) followed by DPPA (0.3 mL, 1.39mmol) under argon atmosphere at 0^{o}C and the resulting reaction mixture was stirred at 100°C for 3 h. Reaction mixture was monitored by TLC [(TLC silica gel plate), mobile phase: 40% ethyl acetate in petroleum ether, 0.5 R_f, UV active]). After completion of starting material, reaction mixture was evaporated under reduced pressure to obtain crude compound which was purified by flash column chromatography by eluting with 10-20% ethyl acetate in petroleum ether and the compound fractions were concentrated under reduced pressure to get 6-amino-1-hydroxyanthracene-9,10-dione (**8**) (100 mg, 45%) as yellow solid. IR (KBr pellet)υ_{max}: 3443, 3367, 2924, 2853, 1631, 1596, 1465, 1367, 1271, 1242, 1188, 1157, 1112, 1036, 960, 908, 829, 810, 754, 716, 676, 523; Melting Range: 278-282^{o}C; ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 12.95 (s, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 7.78 (d, *J* = 7.2 Hz, 1H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.42 (d, *J* = 2.4 Hz, 1H), 7.28 (d, *J* = 7.6 Hz, 1H), 6.95 (dd, *J* = 8.4 Hz, 2.4 Hz, 1H), 4.48 (brs, 2H); ESI-MS: 240.06 (MH)+.

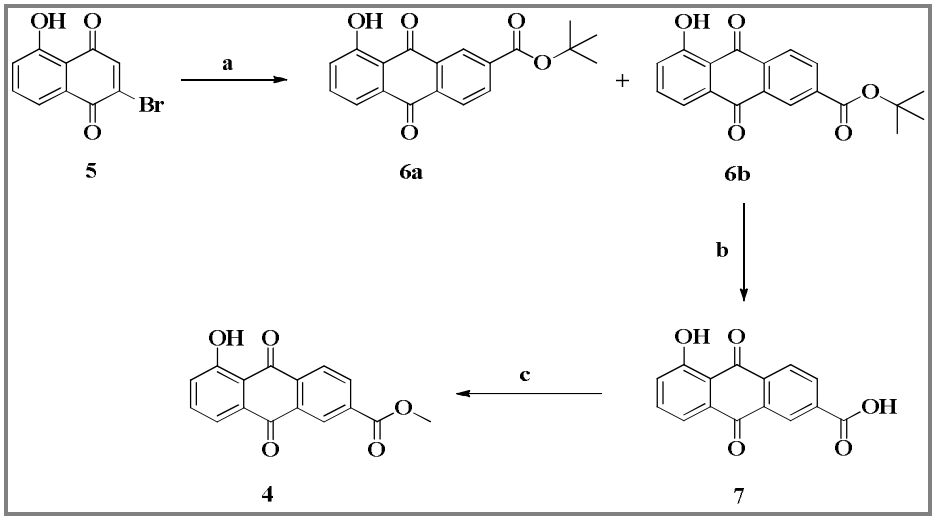
Synthesis of 6-Bromo-1-hydroxyanthracene-9,10-dione (9): To a suspension of Cu(I)Br (150 mg, 1.045 mmol) in acetonitrile (5 ml) was added *iso*-amyl nitrite (0.14 mL, 1.045 mmol) followed by a solution of 6-amino-1-hydroxyanthracene-9,10-dione **(8)** (100 mg, 0.418 mmol) in THF (5 mL) drop wise at 0°C under argon atmosphere and the resulting reaction mixture was stirred at 27 ^{o}C for 4 h. Reaction mixture was monitored by TLC [(TLC silica gel plate), mobile phase: 20% ethyl acetate in petroleum ether, 0.6 R_f, UV active]). After completion of starting material, reaction mixture was diluted with water (25 mL), extracted with ethyl acetate (2x25 mL). The combined organic layer was washed with brine solution (20 mL), dried over Na_2SO_4, evaporated the solvent under reduced pressure to obtain crude compound which was purified by flash column chromatography by eluting with 10-20% ethyl acetate in petroleum to get 7-bromo-1-hydroxyanthracene-9,10-dione (**9**) (40 mg, 32%) as yellow solid. IR (KBr pellet)υ_{max}: 3426, 3081, 2924, 2853, 1700, 1673, 1637, 1580, 1453, 1410, 1384, 1368, 1349, 1285, 1255, 1224, 1152, 1106, 1028, 907, 857, 827, 797, 762, 708, 679,

670,615, 502; Melting Range: 188-191°C; ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 12.52 (s, 1H), 8.43 (d, *J* = 2 Hz, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 7.94 (dd, *J* = 8.4 Hz, 2.0 Hz, 1H), 7.84 (dd, *J* = 7.6 Hz, 1.2 Hz, 1H), 7.70 (t, *J* = 8.0 Hz, 1H), 7.34 (dd, *J* = 8.4 Hz, 1.2 Hz, 1H); ESI-MS: 302.11 (M)+.

Synthesis of Barleriaquinone-I Isomer(3): To a solution of 6-bromo-1-hydroxyanthracene-9,10-dione (**9**) (20 mg, 0.066 mmol) in dioxane:H_2O (4:1, 5 mL) were added K_2CO_3 (45.5 mg, 0.33 mmol), methylboronic acid (11.8 mg, 0.198 mmol) and 1,1′-bis (diphenylphosphino) ferrocene] dichloropalladium(II).CH_2Cl_2 complex (5.3 mg, 0.0066 mmol) under argon atmosphere at 27°C, degassed with argon gas for 10 min and the resulting reaction mixture was stirred at 100°C for 16 h. Reaction mixture was monitored by TLC [(TLC silica gel plate), mobile phase: 20% ethyl acetate in petroleum ether, 0.5 R_f, UV active]). After completion of starting material, reaction mixture was diluted with ethyl acetate (20 mL), filtered through Celite bed and the filtrate was washed with water (2x20 mL), brine solution (20 mL), dried over Na_2SO_4, evaporated organic solvent under reduced pressure to obtain crude compound which was purified by prep TLC by eluting with 10-20% ethyl acetate in petroleum ether to give Barleriaquinone-I Isomer (**3**) (8 mg, 53%) as yellow solid. IR (KBr pellet)υ_{max}: 3785, 3419, 2924, 2854, 1642, 1383, 1260, 1107, 1037, 764, 750, 713, 617; Melting Range: 123-127°C; ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 12.68 (s, 1H), 8.22 (d, *J* = 8.0 Hz, 1H), 8.09 (s, 1H), 7.83 (d, *J* = 7.6 Hz, 1H), 7.66 (t, *J* = 7.6 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.31 (dd, *J* = 7.6 Hz, 0.8 Hz, 1H), 2.54 (s, 3H); ESI-MS: 239.26 (MH)+.

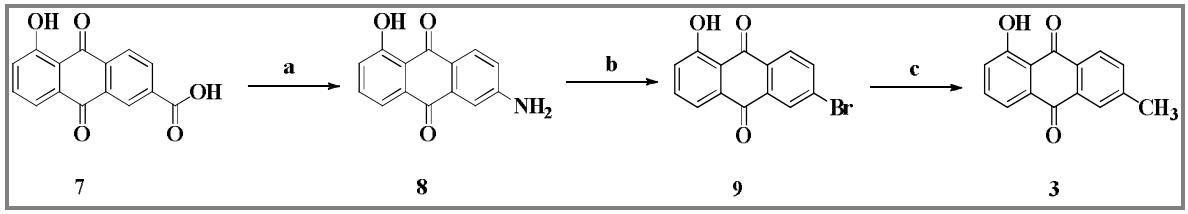
RESULTS AND DISCUSSION

Our synthetic strategy began with bromo compound **5**which on concurrent Heck and cross coupling reaction with *t*-butyl acrylate afforded mixture of regioisomers**6a** and **6b** in 3:7 ratio which were separated by SFC purification method and structures of both the compounds were established by extensive 2D NMR spectral studies [5]. Further hydrolysis of *t*-butyl ester **6b** gave carboxylic acid **7** which was esterified to give Barleriaquinone-II Isomer (**4**) in good yield (Scheme 1).



Scheme 1. Reagents and conditions: (a) Tri-*o*-tolylphosphine, palladium(II) acetate trimer, *t*-butyl acrylate, Et_3N, DMF, 110°C, 16h, **6a** (14%), **6b** (40%); (b) LiOH.H_2O, EtOH, THF, H_2O, rt,48h, 96%; (c) H_2SO_4, MeOH, 75°C, 10h, 76%.

Synthesis of compound **3** was attemptedfrom the carboxylic acid **7** which on Curtius reactionwith DPPA and Et_3N in toluene afforded amine **8** in 45% yield which was converted to bromo compound **9** using Sandmeyer-like reaction with *iso*-amyl nitrite in 32% yield. Lastlybromo compound **9** was converted to Barleriaquinone-I Isomer (**3**) in decent yieldon treatment with methylboronic acid in the presence of Pd(dppf)Cl_2.CH_2Cl_2catalyst (Scheme 2).



Scheme 2. Reagents and conditions:(a)DPPA, Et_3N, toluene, 100°C, 3h, 45%; (b) Cu(I)Br, *iso*-amyl nitrite, CH_3CN, THF, 27°C, 4h, 32%; (c) $CH_3B(OH)_2$, $Pd(dppf)Cl_2.CH_2Cl_2$, K_2CO_3, dioxane, H_2O, 100°C, 16h, 53%.

CONCLUSION

In conclusion, synthesis of regioisomers of Barleriaquinones-I and II was demonstrated via simultaneous Heck and cross coupling reaction as the key step.

ACKNOWLEDGEMENTS

The authors are thankful to GVK Biosciences Private Limited management for constant encouragement and providing facilities for accomplishing this research. Help from the analytical department for all spectroscopic analysis is highly appreciated. We are grateful to Dr. Sudhir Kumar Singh (Chief Operating Officer, GVK Biosciences) for his immense support and motivation. We are also thankful to AU, Visakhapatnam.

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