Synthesis of Imidazolo[5,4-*b*]carbazole-4,10-quinones

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Abstract: The preparation of imidazolo[5,4-*b*]carbazole-4,10-quinones **9** is described. The key steps of the synthesis are selective halogen-metal exchanges on the imidazole **3** and subsequent addition to carbonyl groups of ethyl-3-formylindole-2-carboxylate **4**.

Key words: quinone, imidazole, ellipticine, metalation

The carbazole-1,4-quinone skeleton is encountered in natural products such as murrayaquinone A,[1] calothrixins A and B,[2] koeniginequinones A and B,[3] clausenaquinone-A[4] and related synthetic derivatives (isoellipticine quinone, indolocarbazole quinone, benzo[*b*]carbazole quinone).[5–7] These compounds are a subject of interest because of their remarkable biological activities such as anticancer, antibacterial and antimalarial effects. The pharmacological interest of the carbazole-1,4-quinone derivatives required the development of diverse synthetic approaches (palladium catalysed reactions, Diels–Alder reactions and anionic reactions, among others).[8–10]

In this report, we describe the preparation of new imidazolo[5,4-*b*]carbazole-4,10-quinones from 4,5-diiodo-imidazoles **3** and ethyl-3-formylindole-2-carboxylate (**4**). Our synthetic strategy was based on the ease of effecting halogen-metal exchanges on the imidazole nucleus to produce successively two nucleophilic entities. A similar pathway was envisaged by Gribble but failed for the synthesis of isoellipticine quinone.[5] This approach contrasts with the usual way involving a 'combined directed ortho-metalation and cross-coupling strategy' (Figure 1).[11]

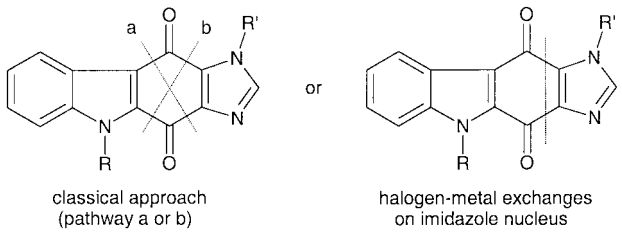
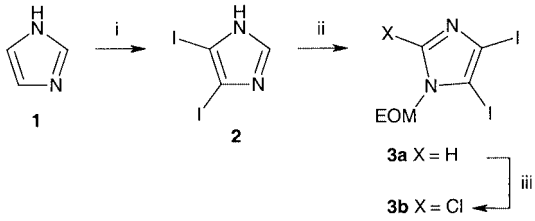


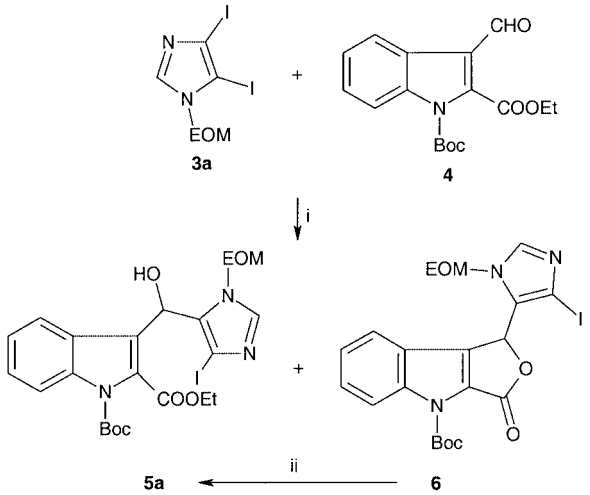
Figure 1

The starting materials **3** for the current work were synthesised by adapting standard methods. Commercially available imidazole **1** was diiodinated with I_2–KI–NaOH, and the resulting 4,5-diiodide **2** was *N*-protected in the presence of K_2CO_3 and $EtOCH_2Cl$ in DMF to give **3a**[12] in 52% yield. Deprotonation at position-2 of **3a** with LDA (1.1 equiv), followed by addition of freshly recrystallised hexachloroethane afforded **3b**[13] in 95% yield (Scheme 1).[14]



Scheme 1 Reagents and conditions: i) I_2 (2.2 equiv), KI (2.2 equiv), NaOH aq, r.t., 1 h, 98%; ii) $EtOCH_2Cl$ (1.4 equiv), K_2CO_3, DMF, r.t., 48 h, 52%; iii) a) LDA (1.1 equiv), THF, –78 °C, 30 min; b) Cl_3CCCl_3 (1.4 equiv), THF, –78 °C, 16 h, 95%

Selective halogen-metal exchange at position-5 of **3a** was initially carried out with EtMgBr (1.1 equiv) at 0 °C,[15] then indole **4**[16] was added to the solution to afford a mixture of alcohol **5a** and lactone **6** in 52% combined yield (Scheme 2, Table 1 entry 1). Replacement of the Grignard reagent by BuLi (1 equiv) at –78 °C led to the lone alcohol **5a** in 49% optimised yield.



Scheme 2 Reagents and conditions: i) *Method A :* EtMgBr (1.1 equiv), THF, 0 °C to r.t., 40 min, then **4** (1.1 equiv), r.t., 1 h; *Method B* : BuLi (1 equiv), THF, –78 °C, 5 min, then **4** (1.2 equiv), THF, –78 °C, 45 min; ii) EtONa (2.2 equiv), EtOH, r.t., 1 h, 85%

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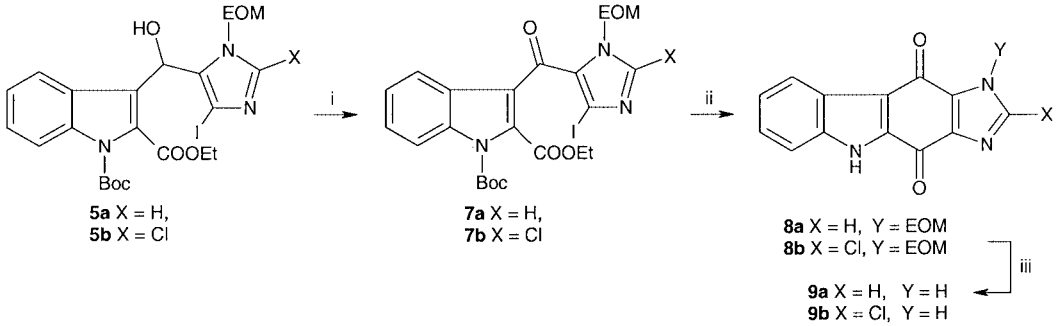
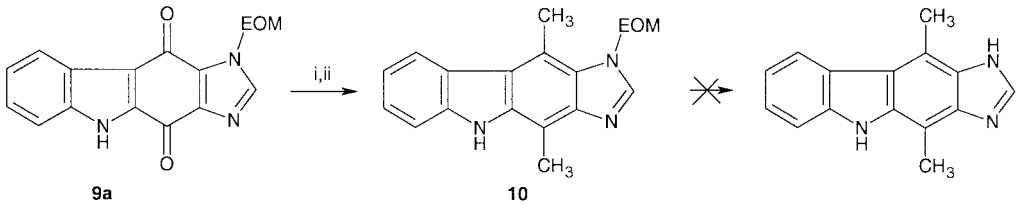


Scheme 3 Reagents and conditions: i) MnO_2 excess, CH_2Cl_2, r.t., 24 h, **7a** = 66%, **7b** = 84%; ii) BuLi (1 equiv), THF, –78 °C, 1 h then r.t., 1 h, **8a** = 48%, **8b** = 52%; iii) 10% HCl aq, 1,4-dioxane, 80 °C, 2 h, **9a** = 80%, **9b** = 83%



Scheme 4 Reagents and conditions: i) MeLi (10 equiv), THF, reflux, 3 h; ii) $NaBH_4$ excess, EtOH, reflux, 18 h, 35%

It is noteworthy that better coupling yield (83%, drawing not shown) was obtained when the reaction was performed between *N*-Boc-3-formylindole and imidazole **3a** under the same conditions.

Alternatively, treatment of **6** with EtONa gave **5a** in 85% yield. Following the BuLi-mediated coupling methodology, compound **5b** was prepared from **3b** and **4** in 50% yield.

Table 1 Yields of Compounds **5** and **6**

Method	Imidazole	**5** (%)	**6** (%)
A	**3a**	**5a** (31)	**6** (21)
B	**3a**	**5a** (49)	–
B	**3b**	**5b** (50)	–

The alcohols **5** were oxidised using MnO_2 to give the ketones **7** in 66–84% yield (Scheme 3). The halogen-metal exchange-cyclisation sequence on **7** was carried out in the presence of BuLi in THF at –78 °C because no exchange was observed with EtMgBr. The quinones **8** were obtained in moderate yields (48–52%).[17] The in situ generated lithium ethoxide is responsible for the removal of the Boc group. A one-pot synthesis of quinone **8a** was investigated by successive addition of BuLi (1.1 equiv twice) on **5a**. Unfortunately, the reaction failed to generate more than traces of **8a**. Final EOM deprotection in acidic medium afforded the final tetracyclic derivatives **9** in fair yield.[18]

Quinones **9** are also important intermediates in the synthesis of imidazolo analogues of ellipticine (Scheme 4). Thus, treatment of **9a** with MeLi and then with $NaBH_4$[5,6] afforded **10**[19] in 35% yield (unoptimised). Surprisingly, we were not able to remove the ethoxymethyl protecting group in compound **10** using several acidic conditions such as aq HCl in 1,4-dioxane, aq HBr or HBr in HOAc. Further experiments are planned to perform this deprotection.

In summary, we have described the preparation of a new series of compounds using an unusual strategy based on selective halogen-metal exchanges on the imidazole nucleus. Cytotoxic properties of compounds **8**–**10** will be the subject of forthcoming investigations.[20]

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(13) Selected data for **3b**: Yellow solid; mp 69–70 °C. IR (KBr): 1460, 1173, 1102 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.21 (t, *J* = 7.0 Hz, 3 H, CH_3), 3.55 (q, *J* = 7.0 Hz, 2 H, CH_2), 5.37 (s, 2 H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.9 (CH_3), 65.0 (CH_2), 77.2 (CH_2), 83.2 (Cq), 94.8 (Cq), 134.3 (Cq). MS (ESI): *m*/*z* = 413 [M + H^+] for ^{35}Cl, 415 [M + H^+] for ^{37}Cl.

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(16) Using standard conditions (esterification, Vilsmeier–Haack formylation, *N*-Boc-protection) the indole derivative **4** was prepared from commercially available indole-2-carboxylic acid in 94% overall yield.

(17) **Typical Procedure for Cyclisation:** To a solution of **7a** (131 mg, 0.2 mmol) in anhyd THF (5 mL), was dropwise added at –78 °C a 2.24 M solution of BuLi in hexanes (103 µL, 0.2 mmol). After 1 h at –78 °C, the reaction mixture was allowed to warm to r.t. and was then hydrolysed by a sat. aq solution of NH_4Cl. The solution was extracted with CH_2Cl_2 (3×), the combined organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude residue was purified by flash chromatography on silica gel (CH_2Cl_2–MeOH, 98:2) to afford quinone **8a** as a red solid in 48% yield. Mp >210 °C (MeOH). IR (KBr): 1676, 1649 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 1.12 (t, *J* = 7.0 Hz, 3 H, CH_3), 3.58 (q, *J* = 7.0 Hz, 2 H, CH_2), 5.75 (s, 2 H, CH_2), 7.28–7.38 (m, 2 H, H_{Ar}), 7.52 (d, *J* = 8.0 Hz, 1 H, H_{Ar}), 8.06 (d, *J* = 8.0 Hz, 1 H, H_{Ar}), 8.28 (s, 1 H, H_{Ar}), 12.99 (s, 1 H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 14.7 (CH_3), 64.2 (CH_2), 74.8 (CH_2), 113.9 (CH), 115.3 (Cq), 121.4 (CH), 123.8 (Cq), 124.0 (CH), 125.9 (CH), 132.6 (Cq), 137.1 (Cq), 137.6 (Cq), 141.9 (Cq), 143.8 (CH), 173.6 (Cq), 174.6 (Cq). MS (ESI): *m*/*z* = 296 [M + H^+]. HRMS (CI): *m*/*z* calcd for $C_{16}H_{14}N_3O_3$: 296.1035; found: 296.1035. Compound **8b** was prepared similarly starting from **7b** but was crystallised from MeOH after chromatography. Red solid; mp >210 °C (MeOH). IR (KBr): 1670, 1650 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 1.20–1.27 (m, 3 H, CH_3), 3.65–3.73 (m, 2 H, CH_2), 5.83 (s, 2 H, CH_2), 7.47–7.50 (m, 1 H, H_{Ar}), 7.98–8.05 (m, 2 H, H_{Ar}), 8.22 (d, *J* = 7.2 Hz, 1 H, H_{Ar}), 9.50 (s, 1 H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 14.8 (CH_3), 64.6 (CH_2), 74.0 (CH_2), 114.1 (CH), 115.2 (Cq), 121.5 (CH), 123.9 (Cq), 124.4 (CH), 126.2 (CH), 133.7 (Cq), 136.5 (Cq), 137.7 (Cq), 139.2 (Cq), 139.8 (Cq), 172.6 (CO), 173.9 (CO). MS (ESI): *m*/*z* = 330 [M + H^+] for ^{35}Cl, 332 [M + H^+] for ^{37}Cl. HRMS (CI): *m*/*z* calcd for $C_{16}H_{13}ClN_3O_3$: 330.0645; found: 330.0645.

(18) Compounds **9** have been characterised by ^1H NMR, ^{13}C NMR (except carbonyl signals), IR, MS and HRMS.

(19) Selected data for **10**: Mp >210 °C (MeOH). ^1H NMR (acetone-d_6): δ = 1.12 (t, *J* = 7.0 Hz, 3 H, CH_3), 2.81 (s, 3 H, CH_3), 3.21 (s, 3 H, CH_3), 3.56 (q, *J* = 7.0 Hz, 2 H, CH_2), 5.84 (s, 2 H, CH_2), 7.15 (t, *J* = 7.9 Hz, 1 H, H_{Ar}), 7.35 (t, *J* = 7.9 Hz, 1 H, H_{Ar}), 7.49 (d, *J* = 7.9 Hz, 1 H, H_{Ar}), 8.15 (s, 1 H, H_{Ar}), 8.29 (d, *J* = 7.9 Hz, 1 H, H_{Ar}), 10.05 (s, 1 H, NH). ^{13}C NMR (acetone-d_6): δ = 11.5 (CH_3), 15.0 (CH_3), 15.2 (CH_3), 63.6 (CH_2), 76.4 (CH_2), 107.0 (Cq), 111.2 (CH), 113.8 (Cq), 118.9 (CH), 120.6 (Cq), 123.3 (CH), 125.4 (Cq), 125.5 (CH), 128.3 (Cq), 137.5 (Cq), 142.6 (Cq), 144.7 (Cq), 146.5 (CH). MS (ESI): *m*/*z* = 294 [M + H^+]. HRMS (CI): *m*/*z* calcd for $C_{18}H_{20}N_3O$: 294.1606; found: 294.1606.

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