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Synthesis of aryl ring-fused benzimidazolequinones using 6-*exo-trig* radical cyclizations

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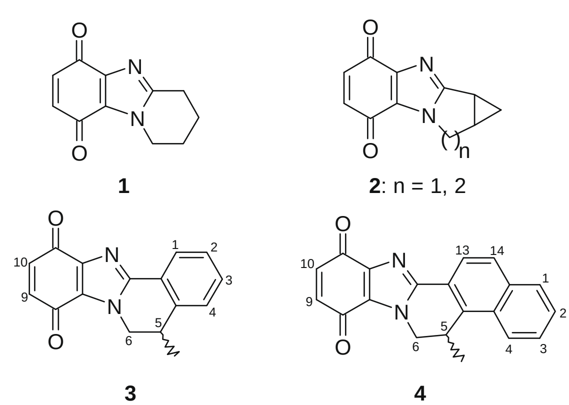
The preparation of alicyclic ring-fused tetracyclic and pentacyclic benzimidazoles containing one and two fused aryl rings, respectively, is achieved conveniently in three steps, including Bu_3SnH-mediated 6-*exo-trig* cyclization of σ-aryl radicals generated from 1-allyl-2-(ω-bromoaryl)benzimidazoles. Inclusion of 4,7-dimethoxy substituents on the radical precursors allows access to aryl ring-fused benzimidazolequinones, a unique family of potential bioreductive anti-cancer agents.

Many benzimidazolequinones have been reported to exhibit potent anti-cancer activity.[1–5] This is thought to be initiated by bioreduction of the quinone moiety either by single electron transfer (SET) to give a semiquinone radical,[3,6–8] or by two-electron transfer to give the hydroquinone.[1,9] Recently, we reported the synthesis of [1,2-*a*] alicyclic ring-fused benzimidazolequinones, such as **1** and **2** (Fig. 1), which were shown to possess cytotoxicity towards normal human fibroblast cells in the nanomolar range (10^{-9} M).[3] Moreover, the only known alicyclic ring-fused tetracyclic benzimidazolequinones are the cyclopropane-fused compounds reported by our group (e.g., **2**).[6–8] We now report the synthesis of a new class of benzimidazolequinones containing additional fused aryl rings; 5-methyl-5,6-dihydrobenzimidazo[2,1-*a*]isoquinoline-8,11-dione **3** and 5-methyl-5,6-dihydrobenzimidazo[2,1-*a*]benzo[*f*]isoquinoline-8,11-dione **4** containing one and two aryl rings, respectively. The increased conjugation offered by the aryl ring(s) is expected to facilitate reductive activation by imparting greater stabilization to the biologically active reduced intermediates. The described concise synthesis of these new heterocyclic systems includes a new 6-*exo-trig* cyclization of σ-aryl radicals generated from the reaction of 1-allyl-2-(ω-bromoaryl)-1*H*-benzimidazole with $Bu_3Sn^{\cdot}$.

Initial investigations focused on the synthesis of non-functionalized benzimidazo[2,1-*a*]isoquinoline **9a** (Scheme 1) and benzimidazo[2,1-*a*]benzo[*f*]isoquinoline **12a** (Scheme 2), before preparing compounds with appropriately placed dimethoxy substituents for conversion into benzimidazolequinones. The synthesis began with condensation of 2-bromobenzoic acid or 1-bromo-2-naphthoic acid with (3,6-dimethoxy)benzene-1,2-diamine in polyphosphoric acid (PPA), according to a modification of the literature method for preparing 2-(2-bromophenyl)-1*H*-benzimidazole **5a**.[10] Multi-gram quantities of aryl bromides were obtained in 50–76% yield, including novel benzimidazoles **5b** and **10a,b**. N-Alkylation of benzimidazoles **5a**,**b** and **10a**,**b** with sodium hydride and 3-bromoprop-1-ene in THF gave novel compounds **6a**,**b** and **11a**,**b** in 68–88% yield.

Initial radical cyclization attempts involved the addition of a solution of Bu_3SnH (1.4 equiv) and 1,1′-azobis(cyclohexanecarbonitrile) (ACN) (0.2 equiv) in toluene (50 ml) over 8 h to a refluxing toluene solution of **6a** (32 mM) (Scheme 1).[11] This gave mainly ring-closed compound **9a**, but also reduced non-cyclized, 1-al-



1 **2**: n = 1, 2 **3** **4**

Figure 1.

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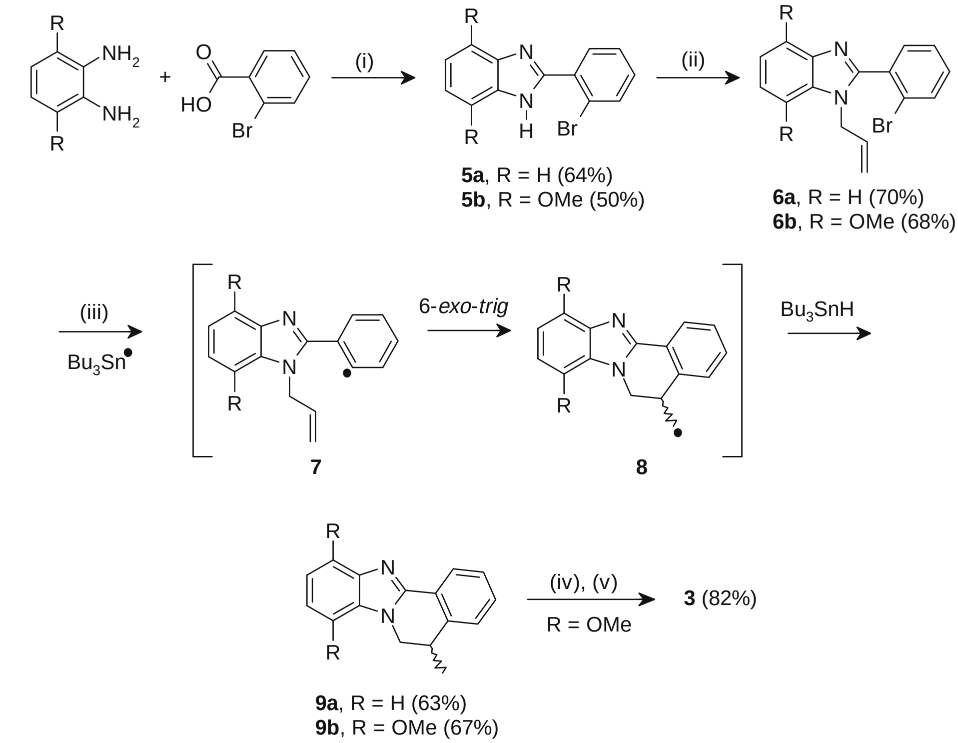
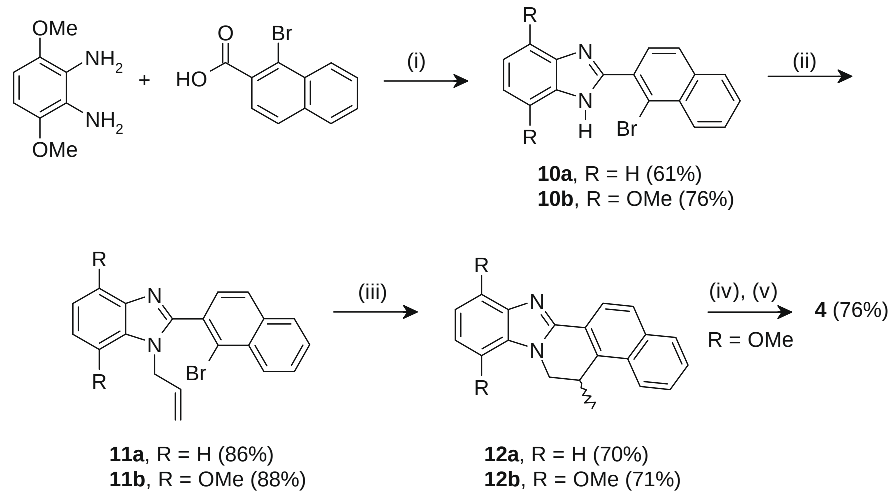


Scheme 1. Reagents and conditions; (i) PAA, 150 °C, 6 h; (ii) NaH, THF, $CH_2{=}CHCH_2Br$, reflux, 4 h; (iii) Bu_3SnH (1.4 equiv), ACN (0.2 equiv), 8 h, PhMe, reflux; (iv) 48% HBr (aq), reflux, 3 h; (v) $FeCl_3$ (aq), rt, 18 h.



Scheme 2. Reagents and conditions; (i) PAA, 150 °C, 6 h; (ii) NaH, THF, $CH_2{=}CHCH_2Br$, reflux, 4 h; (iii) Bu_3SnH (1.4 equiv), ACN (0.2 equiv), 8 h, PhMe, reflux; (iv) 48% HBr (aq), reflux, 3 h; (v) $FeCl_3$ (aq), rt, 18 h.

lyl-2-phenyl-1*H*-benzimidazole[12] (11:1 by ^{1}H NMR). The product mixture was found to be inseparable by chromatography, and cyclized compound **9a** was separated by precipitating its HBr salt from acetonitrile. An aqueous basified solution of **9a** was then extracted with dichloromethane giving the isolated free base in 63% yield. The efficiency of this radical cyclization is exemplified by carrying out the reaction without the slow syringe pump addition of Bu_3SnH and ACN. The high concentration of Bu_3SnH should favour reduction of reactive σ-aryl radical **7** over cyclization to the more stable radical **8**, however, the ^{1}H NMR spectrum showed a 6:1 ratio of **9a** to 1-allyl-2-phenyl-1*H*-benzimidazole. Annulations via metal hydride-mediated chain reactions using 6-*exo-trig* cyclization of aryl radicals are under-utilized in synthesis[13–16] compared with widely used non-chain homolytic aromatic substitutions,[17] including cyclizations onto diazoles[3] that require large amounts of radical initiators to give aromatic products. Schemes 1 and 2 show that subjecting bromides **6b** and **11a**,**b** to an analogous 8 h addition of Bu_3SnH (1.4 equiv) and ACN (0.2 equiv) gave the required cyclized compounds, 8,11-dimethoxy-5-methyl-5,6-dihydrobenzimidazo[2,1-*a*]isoquinoline **9b** and 5-methyl-5,6-dihydrobenzimidazo[2,1-*a*]benzo[*f*]isoquinolines **12a**[18] and **12b** in about 70% yields.

Formation of quinones **3**[19] and **4** via hydrobromic acid induced demethylation of the 8,11-dimethoxy substituents of **9b** and **12b** and in situ oxidation of the reactive hydroquinones occurred in 76% and 82% yield, respectively, using a reported procedure.[3,6,7]

In conclusion, an efficient 6-*exo-trig* cyclization of σ-aryl radicals has allowed access to new alicyclic ring-fused tetracyclic and pentacyclic benzimidazoles and benzimidazolequinones. We are currently extending this annulation to other σ-aryl and heterocyclic radicals to give further novel ring-fused benzimidazolequinones.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.07.023.

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11. *5-Methyl-5,6-dihydrobenzoimidazo[2,1-a]isoquinoline* (**9a**): Bu_3SnH (0.625 g, 2.2 mmol) and ACN (78 mg, 0.32 mmol) in PhMe (50 ml) were added over 8 h via syringe pump to *N*-allyl-2-(2-bromophenyl)-1*H*-benzimidazole **6a** (0.500 g, 1.6 mmol) in PhMe (50 ml) at reflux. The cooled solution was evaporated to dryness and purified by column chromatography using silica as absorbent with gradient elution (hexane–EtOAc) to give an inseparable mixture of **9a** and 1-allyl-2-phenyl-1*H*-benzimidazole. HBr was added to the residue in acetonitrile (10 ml) until the bromide salt of **9a** precipitated. The salt was dissolved in water and Na_2CO_3 added until pH 8. The free diazole base was extracted with CH_2Cl_2 and evaporated to dryness to give **9a** (0.236 g, 63%) as a colourless oil; R_f 0.58 (1:1 EtOAc:hexane); ^1H NMR (399.78 MHz, $CDCl_3$) δ 8.31–8.29 (m, 1H, Ar-H), 7.84–7.82 (m, 1H, 11-H), 7.42–7.37 (m, 2H, Ar-H), 7.34–7.29 (m, 2H, 8-H, Ar-H), 7.28–7.25 (m, 2H, 9,10-H), 4.27 (dd, J^2 = 12.2 Hz, J^3 = 5.0 Hz, 1H, 6-H*H*), 4.04 (dd, J^2 = 12.2 Hz, J^3 = 5.7 Hz, 1H, 6-*H*H), 3.39–3.34 (m, 1H, 5-H), 1.34 (d, *J* = 6.9 Hz, 3 H, Me); ^{13}C NMR (100.53 MHz, $CDCl_3$) δ 148.7, 143.9, 139.5, 134.8 (all C), 130.3, 127.5, 126.6, 125.6 (all Ar-CH), 125.5 (C), 122.5 (Ar-CH), 122.3 (Ar-CH), 119.6 (11-CH), 108.9 (8-CH), 46.6 (CH_2), 32.7 (5-CH), 19.4 (Me);[20] IR (neat): ν = 1228, 1264, 1287, 1325, 1408, 1481, 1529, 1615 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{16}H_{14}N_2$: 234.1152; found: 234.1147 $[M]^+$.
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18. *5-Methyl-5,6-dihydrobenzimidazo[2,1-a]benzo[f]isoquinoline* (**12a**): 1-Allyl-2-(1-bromo-2-naphthyl)-1*H*-benzimidazole **11a** (1.000 g, 2.7 mmol), Bu_3SnH (1.060 g, 3.7 mmol) and ACN (0.133 g, 0.5 mmol) gave **12a** (0.540 g, 70%) as a white solid; R_f 0.45 (1:1 EtOAc:hexane); mp 191–192 °C; ^1H NMR (399.78 MHz, $CDCl_3$) δ 8.43 (d, *J* = 8.6 Hz, 1H, Ar-H), 8.11 (d, *J* = 8.2 Hz, 1H, Ar-H), 7.92–7.86 (m, 3H, 11-H, Ar-H), 7.62–7.53 (m, 2H, Ar-H), 7.43–7.40 (m, 1H, 8-H), 7.33–7.30 (m, 2H, Ar-H), 4.43 (dd, J^2 = 12.2 Hz, J^3 = 0.9 Hz, 1H, 6-H*H*), 4.34 (dd, J^2 = 12.2 Hz, J^3 = 4.6 Hz, 1H, 6-*H*H); 4.18–4.11 (m, 1H, 5-H), 1.37 (d, *J* = 7.4 Hz, 3H, Me); ^{13}C NMR (100.53 MHz, $CDCl_3$) δ 149.3, 144.5, 136.5, 135.4, 134.8, 130.3 (all C), 129.4, 128.2, 127.2, 126.9, 123.3, 122.9, 122.8 (all Ar-CH), 122.7 (C), 122.6 (Ar-CH), 199.9 (11-CH), 109.1 (8-CH), 46.7 (CH_2), 29.1 (5-CH), 20.3 (Me);[20] IR (neat): ν = 1173, 1244, 1322, 1410, 1446, 1474, 1507 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{20}H_{17}N_2$: 285.1392; found: 285.1394 $[M+H]^+$.
19. *5-Methyl-5,6-dihydrobenzimidazo[2,1-a]isoquinoline-8,11-dione* (**3**): 8,11-Dimethoxy-5-methyl-5,6-dihydrobenzimidazo[2,1-*a*]isoquinoline **9b** (0.500 g, 1.7 mmol), 48% hydrobromic acid (15 ml) and aq $FeCl_3$ solution (0.7 M, 15 ml) gave **3** (0.368 g, 82%) as a red solid; R_f 0.53 (1:1 EtOAc:hexane); mp 181–182 °C; ^1H NMR (399.78 MHz, $CDCl_3$) δ 8.23 (d, *J* = 7.6 Hz, 1H, Ar-H), 7.47–7.33 (m, 3H, Ar-H), 6.68 (AB-q, J^3 = 10.6 Hz, 1H, 10(9)-H), 6.63 (AB-q, J^3 = 10.6 Hz, 1H, 9(10)-H), 4.59 (dd, J^2 = 13.6 Hz, J^3 = 5.3 Hz, 1H, 6-H*H*), 4.46 (dd, J^2 = 13.6 Hz, J^3 = 6.5 Hz, 1H, 6-*H*H), 3.40–3.34 (m, 1H, 5-H), 1.37 (d, *J* = 6.8 Hz, 3H, Me); ^{13}C NMR (100.53 MHz, $CDCl_3$) δ 181.3 (C=O), 178.4 (C=O), 149.2, 142.4, 139.0 (all C), 136.5 (Ar-CH), 136.2 (Ar-CH), 131.4 (Ar-CH), 130.3 (C), 127.9 (Ar-CH), 126.6 (Ar-CH), 126.2 (Ar-CH), 124.1 (C), 48.3 (CH_2), 32.4 (5-CH), 18.9 (Me); IR (neat): ν = 1095, 1195, 1270, 1423, 1460, 1509, 1655 (C=O) cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{16}H_{13}N_2O_2$: 265.0977; found: 265.0974 $[M+H]^+$.
20. Assignments for compounds **9a** and **12a** are supported by HMQC ^1H–^{13}C NMR 2D spectra. DEPT analysis was carried out on all compounds.