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Palladium-catalyzed synthesis of *o*-acetylbenzoic acids: a new, efficient general route to 2-hydroxy-3-phenyl-1,4-naphthoquinones and indolo[2,3-*b*]naphthalene-6,11-diones

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Abstract—We describe here a new, efficient general synthesis of *o*-acetylbenzoic acids by Heck palladium-catalyzed arylation of *n*-butyl vinyl ether with *o*-bromobenzoic acid esters and the use of these compounds as starting materials for the synthesis of 3-benzylideneisochroman-1,4-diones, which readily rearrange to 2-hydroxy-3-phenyl-1,4-naphthoquinones. The application of this strategy to the synthesis of indolo[2,3-*b*]naphthalene-6,11-diones is also described.

Naphthoquinones are of perennial chemical interest on account of their biological properties, their industrial applications and their potential as intermediates in the synthesis of heterocycles.[1–3] For example, 3-hydroxy-2-phenyl-1,4-naphthoquinones have been used as synthetic precursors of antibiotic and antitumoral quinonoid compounds,[4] including 5*H*-benzo[*b*]carbazole-6,11-diones (indolonaphthoquinones)—a class of indoles that became important synthetic targets when it was proposed that kinamycin antibiotics[5] were *N*-cyano-5*H*-benzo[*b*]carbazole-6,11-diones and, more recently, when the antineoplastic activity of these compounds was established.[6] Antineoplastic activity is also shown by structurally related pyrido-[*b*]carbazoles[7] such as elliptinium, which have well-documented antitumor properties. The antineoplastic activity of these compounds has been attributed to their ring systems, which contain an embedded 2-phenylnaphthalene-like structure in a planar conformation.[8]

We recently described several syntheses of 3-hydroxy-2-phenylnaphthoquinones[9] and some of these routes were simpler and more efficient than previous[10] and more recent[11] syntheses. However, the general applicability of these routes is limited by the methods used to prepare starting materials (Friedel–Crafts[12,13] acylation or Bichler–Napieralski cyclization[9a,b]). We report here our preliminary results on a new, general synthesis of 3-hydroxy-2-phenyl-1,4-naphthoquinones. The approach is based on the rearrangement of 3-benzylideneisochroman-1,4-diones resulting from isochroman-1,4-diones, which in turn are easily prepared from 2-acetylbenzoic acids. This route also allowed us to develop a general synthesis of indolonaphthoquinones (**12**).

Taking into account our previous efficient synthesis of *o*-acetylphenylacetic acids by Heck coupling of *n*-butyl vinyl ether (BVE) and 2-bromophenylacetates,[4a] we reasoned that a similar Heck coupling reaction might give easy access to *o*-acetylbenzoic acids. This was confirmed when the reaction of BVE with methyl *o*-bromobenzoate (**1a**, R = H), under conditions used by Cabri et al.[14] (Scheme 1, Table 1, entry 1), produced the desired α-arylated compound **2a** (α-selectivity being attributed to the inclusion of TlOAc and a chelating phosphine in the reaction medium). Compound **2a** was directly treated with 10% aq. HCl in THF at room temperature for 1 h to produce an almost quantitative yield of ketoester **3a**.[15] Formation of the β-arylated product expected for classical Heck conditions (no TlOAc) was not detected by ^{1}H NMR spectroscopy. Coupling of BVE to the electron-rich bromobenzoate **1b** (R = OMe) gave a lower yield of **3d** even when a longer reaction time was used (Table 1, entry 2), although regioselectivity was again total in this case. Similar regiochemical purities were obtained when these reactions were carried out using classical Heck conditions,[16,17] which require longer reaction times but have the advantage of not involving the use of Tl salts and expensive phosphines (Table 1, entries 3 and 4).

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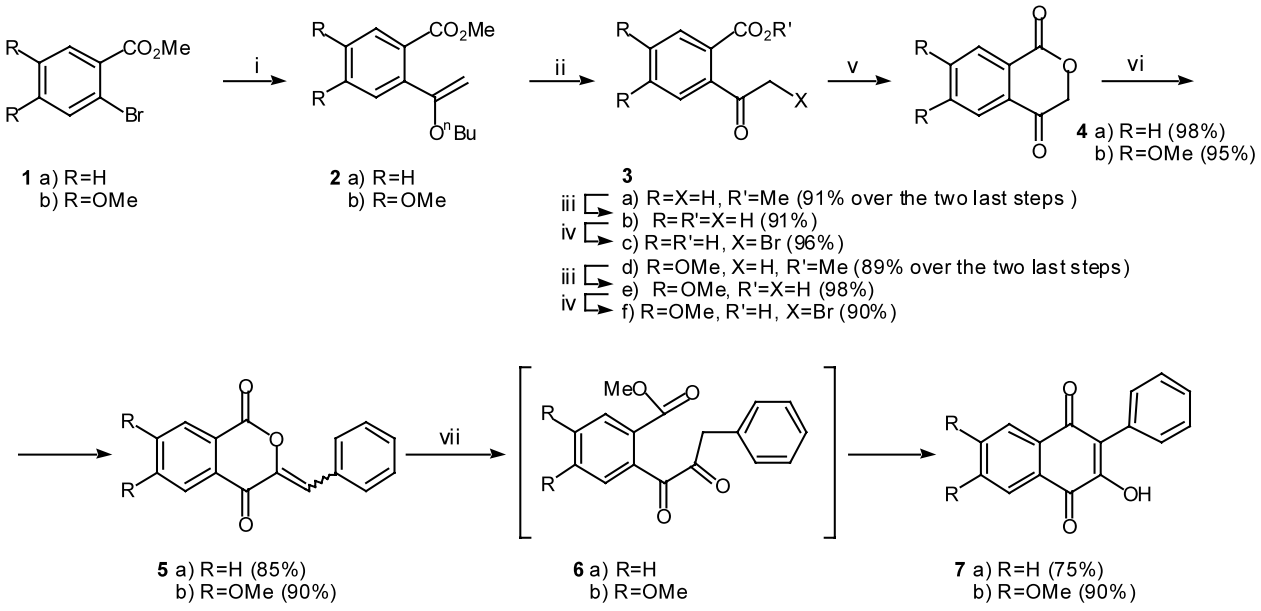


Scheme 1. *Reagents and conditions*: (i) see Table 1. (ii) 10% aq. HCl, rt, 1 h. (iii) 20% aq. H_2SO_4, dioxane, reflux, 2 h. (iv) Br_2, AcOH:toluene (1:2), 60°C, 30 min. (v) NaOAc, EtOH, rt, 30 min. (vi) NH_4OAc, AcOH, 60°C, 6 h. (vii) NaOMe, MeOH, rt, 24 h.

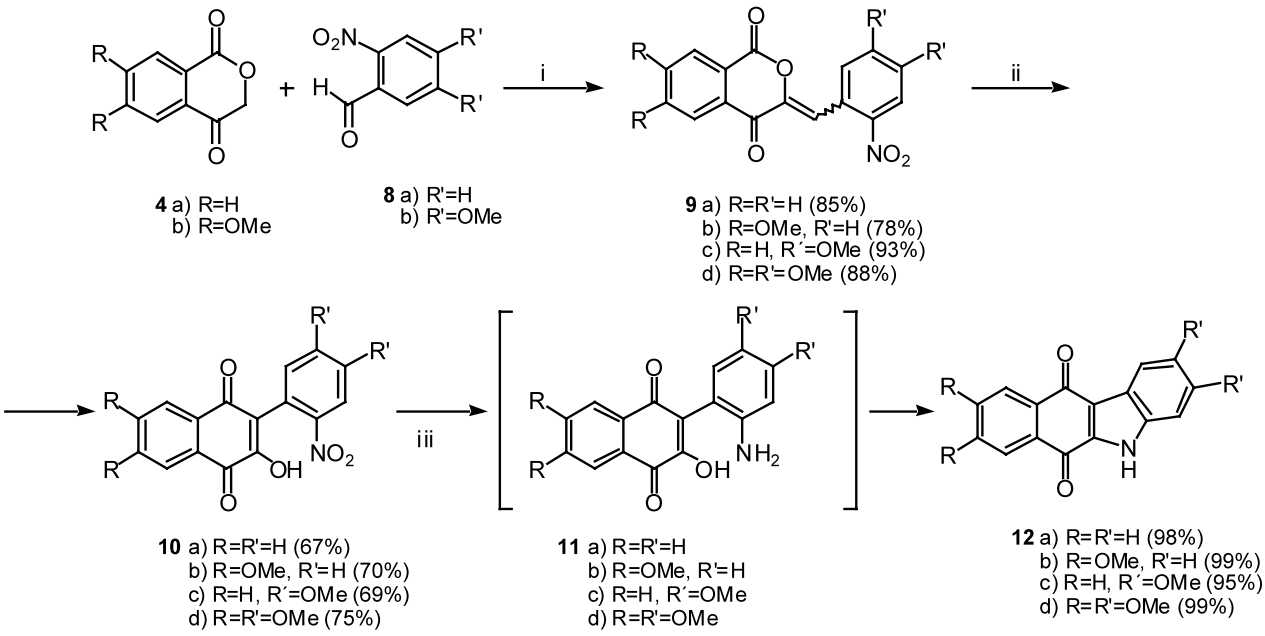
Table 1. Coupling of *o*-bromobenzoates to BVE

Entry	Compound	Catalyst	Additive	Solvent	Reaction time (h)	Reaction product (%)
1	**1a** (R = H)	$Pd(OAc)_2$/DPPP (2.5 mol%)	TlOAc	DMF	2.5	**3a** (90)
2	**1b** (R = OMe)	$Pd(OAc)_2$/DPPP (2.5 mol%)	TlOAc	DMF	3.5	**3d** (85)
3	**1a** (R = H)	$Pd(OAc)_2/Ph_3P$ (7.5 mol%)	–	CH_3CN	4	**3a** (91)
4	**1b** (R = OMe)	$Pd(OAc)_2/Ph_3P$ (7.5 mol%)	–	CH_3CN	16	**3d** (89)

The high α-regioselectivity achieved with classical Heck conditions suggests that the carboxymethyl group of aryl halides **1** interacts with the palladium complex to give a chelate-facilitated α-arylation,[18] a mechanism different from the one hypothesized by Cabri et al.[14] for the arylation of BVE in the absence of TlOAc. As far as we know, this is the second example in which Cabri coupling conditions have facilitated the reaction but are not necessary for α-selectivity.[14]

Next, methyl *o*-acetylbenzoates **3a** and **3d** were hydrolyzed to the corresponding benzoic acids **3b** and **3e**, which were easily converted into 3-hydroxy-2-phenyl-1,4-naphthoquinones **7a** and **7b** through benzylideneisochroman-1,4-diones **5a** and **5b**, respectively. Thus, when *o*-acetylbenzoic acid **3b** was reacted with bromine in acetic acid/toluene (1:2) at 60°C for 30 min, the corresponding 2-bromoacetylbenzoic acid **3c** was obtained. This compound readily cyclizes under basic conditions to give the isochroman-1,4-dione **4a**.[19] Condensation of **4a** with benzaldehyde gave benzylideneisochromanone **5a**, which when stirred with sodium methoxide in methanol at rt for 24 h rearranged to 3-hydroxy-2-phenyl-1,4-naphthoquinone **7a**, probably through benzoic acid ester **6a**.[20] Similarly, phenylnaphthoquinone **7b** was obtained from dimethoxylated *o*-acetylbenzoic acid **3d**, through compounds **3e**, **3f**, **4b** and **5b**.

This easy and efficient method for the preparation of 2-hydroxy-3-phenyl-1,4-naphthoquinones allowed us to develop a new, general synthesis of indolonaphthoquinones **12** (Scheme 2). Condensation of isochroman-1,4-dione **4a** with nitrobenzaldehyde gave the expected nitrobenzylideneisochroman-1,4-dione **9a** and subsequent treatment of this compound with sodium methoxide in methanol afforded nitrophenylnaphthoquinone **10a**. Compound **10a** was converted, as described previously,[4a] into indolonaphthoquinone **12a** by treatment with $NaBH_4$ in isopropanol at rt, a process that presumably takes place via the aminophenylnaphthoquinone intermediate **11a**, with the amino group attacking C_4. The utility of this route was demonstrated by the preparation of indolonaphthoquinones **12b**, **12c** and **12d**. Dimethoxylated indolonaphthoquinone **12b** was obtained from dimethoxylated isochroman-1,4-dione **4b** and *o*-nitrobenzaldehyde, through nitrobenzylideneisochroman-1,4-dione **9b** and nitrophenylnaphthoquinone **10b**, which has previously[4a] been transformed into **12b**. Secondly, isochroman-1,4-dione **4a** and dimethoxylated *o*-nitrobenzaldehyde **8b** were converted into nitrobenzylideneisochromanone **9c**. This compound was then converted into dimethoxylated nitrophenylnaphthoquinone **10c** using a similar route as for **12a**. Finally, rearrangement of nitrobenzylideneisochromanone **9d**—resulting from condensation of dimethoxylated isochromanone **4b** and



Scheme 2. *Reagents and conditions*: (i) NH_4OAc, AcOH, 60°C, 6 h. (ii) NaOMe, MeOH, rt, 24 h. (iii) $NaBH_4$, *i*-PrOH, rt, 6 h.

o-nitrobenzaldehyde **8b**—gave the expected tetramethoxylated nitrophenylnaphthoquinone **10d**, which has previously been used to obtain tetramethoxylated indolonapthoquinone **12d**.[4k]

In conclusion, we have established an efficient method for the preparation of *o*-acetylbenzoic acids, which are convenient starting materials for unrestricted access to isochroman-1,4-diones **4**, benzylideneisochroman-1,4-diones **5**, 2-hydroxy-3-phenyl-1,4-naphthoquinones **7** and indolonaphthoquinones **12**. Work is currently in progress to synthesize a variety of indolonanaphthoquinones for chemical and biological studies. We are also studying the application of this synthetic methodology to the preparation of natural compounds of chemical and biological interest, including the synthesis of compounds related to indolonaphthoquinones, such us ellipticines, benzofuronaphthoquinones and benzopironaphthoquinones, all of which have well-documented antibiotic and/or antitumoral activity.[1]

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15. All new compounds gave satisfactory analytical and spectroscopic data. Selected physical and spectroscopic data follow. Compound **3a** (oil). ^{1}H NMR (250, ppm, $CDCl_3$): 2.83 (s, 3H, -$COCH_3$); 3.89 (s, 3H, -OCH_3); 7.38–7.61 (m, 3H, 3×Ar-H); 7.84 (dd, $J=1$ Hz and $J=7$ Hz, 1H, Ar-H). MS (m/z, %): 262 (M^+,70); 231 (100). Compound **3d**. Mp 119–120°C (ethyl acetate). ^{1}H NMR (250, ppm, $CDCl_3$): 2.42 (s, 3H, -$COCH_3$), 3.81 (s, 3H, -OCH_3), 3.86 (s, 3H, -OCH_3), 3.87 (s, 3H, -OCH_3), 6.79 (s, 1H, Ar-H), 7.28 (s, 1H, Ar-H). MS (m/z, %): 238 (M^+, 21), 223 (100). Compound **5a**. Mp 168–169°C (chloroform/methanol). ^{1}H NMR (250, ppm, $CDCl_3$): 7.17 (s, 1H, -CH), 7.40–7.45 (m, 3H, 3×Ar-H), 7.85–7.99 (m, 4H, 4×Ar-H), 8.22–8.32 (m, 2H, 2×Ar-H). MS (m/z, %): 250 (M^+, 51), 104 (100). Compound **5b**. Mp 250–251°C (chloroform/methanol). ^{1}H NMR (250, ppm, $CDCl_3$): 4.04 (s, 3H, -OCH_3), 4.05 (s, 3H, -OCH_3), 7.16 (s, 1H, -CH), 7.39–7.46 (m, 3H, 3×Ar-H), 7.61 (s, 1H, Ar-H), 7.65 (s, 1H, Ar-H), 7.96–7.99 (m, 2H, 2×Ar-H). MS (m/z, %): 310 (M^+, 83), 282 (100). Compound **7a**. Mp 139–141°C (methanol). ^{1}H NMR (250, ppm, $CDCl_3$): 7.40–7.54 (m, 5H, 5×Ar-H), 7.72–7.85 (m, 2H, 2×Ar-H), 8.15–8.23 (m, 2H, 2×Ar-H). MS (m/z, %): 250 (M^+, 100). Compound **7b**. Mp 253–255°C (methanol). ^{1}H NMR (250, ppm, $CDCl_3$): 4.05 (s, 6H, 2×-OCH_3), 7.41–7.52 (m, 5H, 5×Ar-H), 7.54 (s, 1H, Ar-H), 7.63 (s, 1H, Ar-H). MS (m/z, %): 310 (M^+, 100). Compound **9a**. Mp 186–188°C (chloroform/methanol). ^{1}H NMR (250, ppm, $CDCl_3$): 7.52–7.63 (m, 2H, =CH, Ar-H), 7.70–7.78 (m, 1H, Ar-H), 7.89–7.96 (m, 2H, 2×Ar-H), 8.04–8.13 (m, 2H, 2×Ar-H), 8.26–8.37 (m, 2H, 2×Ar-H). MS (m/z, %): 296 (M^++1, 48), 104 (100). Compound **9b**. Mp 286–287°C (chloroform/methanol). ^{1}H NMR (500, ppm, DMSO): 4.00 (s, 6H, 2×-OCH_3), 7.35, 7.59 and 7.60 (ss, 3H, =CH and 2×Ar-H), 7.66–7.70 (m, 1H, Ar-H), 7.84–7.87 (m, 1H, Ar-H), 8.06–8.08 (m, 1H, Ar-H), 8.11–8.13 (m, 1H, Ar-H). MS (m/z, %): 356 (M^++1, 100). Compound **9c**. Mp 229–230°C (chloroform/methanol). ^{1}H NMR (250, ppm, $CDCl_3$): 4.01 (s, 3H, -OCH_3), 4.05 (s, 3H, -OCH_3), 7.63, 7.68 and 7.70 (ss, 3H, =CH and 2×Ar-H), 7.87–7.97 (m, 2H, 2×Ar–H), 8.27–8.36 (m, 2H, 2×Ar–H). MS (m/z, %): 356 (M^++1, 12), 149 (100). Compound **9d**. Mp 291–292°C (chloroform/methanol). ^{1}H NMR (500, ppm, DMSO): 3.94 (s, 6H, 2×-OCH_3), 4.00 (s, 6H, 2×-OCH_3), 7.42, 7.60, 7.68 and 7.73 (ss, 5H, =CH and 4×Ar-H). MS (m/z, %): 416 (M^++1, 100). Compound **10c**. Mp 251–252°C (methanol). ^{1}H NMR (250, ppm, DMSO): 3.84 (s, 3H, -OCH_3), 3.92 (s, 3H, -OCH_3), 7.10 (s, 1H, Ar-H), 7.73 (s, 1H, Ar-H), 7.84–7.93 (m, 2H, 2×Ar-H), 7.96–8.03 (m, 1H, Ar-H), 8.06–8.12 (m, 1H, Ar-H). MS (m/z, %): 356 (M^++1, 27), 149 (100). Compound **12c**. Mp 275–277°C (methanol). ^{1}H NMR (250, ppm, DMSO): 3.66 (s, 3H, -OCH_3), 3.75 (s, 3H, -OCH_3), 6.63 (s, 1H, Ar-H), 6.81 (s, 1H, Ar-H), 7.60–7.75 (m, 2H, 2×Ar-H), 7.92–8.02 (m, 2H, 2×Ar-H). MS (m/z, %): 307 (M^+, 64), 66 (100).
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17. General procedure. A solution of 1.2 mmol of **1**, 6 mmol of BVE, 0.09 mmol of $Pd(OAc)_2$ (7.5 mol%), 0.18 mmol of Ph_3P (Pd/ligand ratio 1:2) and 1.44 mmol of Et_3N in 2.5 mL of dry degassified acetonitrile was heated at 100°C in a screw-capped Pyrex tube for the stated time. The solution was cooled, filtered through Celite and washed with water (25 mL). The solvents were evaporated and a sample was examined by ^{1}H NMR spectroscopy. The crude material was dissolved in a 1:1 mixture of 10% aq. HCl and THF (40 mL) and the solution stirred for 1 h at rt. The THF was removed under vacuum and the residue was extracted with CH_2Cl_2. The extracts were washed with water until pH 7 was reached and dried with anhydrous Na_2SO_4, and the solvents were removed. The stated yield of the reaction is the yield after purification by flash chromatography on silica gel.
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