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1,2- and 1,4-Naphthoquinones: general synthesis of benzo[*b*]naphtho[2,3-*d*]furan-6,11-diones

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Abstract

A new general synthesis of benzo[*b*]naphtho[2,3-*d*]furan-6,11-diones starting from readily available 2-(2′-oxo-3′-phenylpropyl)benzaldehydes is described.

Keywords: antitumour compounds; furans; quinones; Ullmann reactions.

Naphthoquinones[1] are of perennial chemical interest on account of their biological properties, their industrial applications and their potential as intermediates in the synthesis of heterocycles such as benzo[*b*]furonaphthoquinones (**8**)[2]. The latter, of known industrial interest, have recently become interesting synthetic targets due to the high activity shown in various biological tests.[3] We recently described two closely related syntheses of benzofuronaphthoquinones. Both were simpler and more efficient than previous syntheses, but of limited scope because of the limited availability of the required starting materials.[4] Here we report preliminary results on a more convenient synthesis of benzofuronaphthoquinones[5] **8** via the corresponding 3-hydroxy-2-phenyl-1,4-naphthoquinones **10**, which are easily prepared from 2-(2′-oxo-3′-phenylpropyl)benzaldehydes **5** (Scheme 1).

2-(2′-Oxo-3′-phenylpropyl)benzaldehyde **5a** was easily and efficiently obtained by aldol condensation of 1-indanone and *o*-bromobenzaldehyde followed by sequential reduction and dehydration of benzylideneindanone **3a** and ozonolysis of the resulting indene **4a**. Intramolecular aldol condensation of **5a** and subsequent dehydration of the resulting aldol produced naphthol **6a**, which was easily oxidized to the *o*-quinone **9a**. Treatment of this latter with H_2SO_4 afforded 2-hydroxynaphthoquinone **10a**, which readily gave benzofuronaphthoquinone **8a** when subjected to standard Ullmann coupling conditions. It was subsequently found possible to obtain **8a** more directly by oxidation of benzonaphthofuran **7a**, the product of Ullmann reaction of bromophenylnaphthol **6a**.

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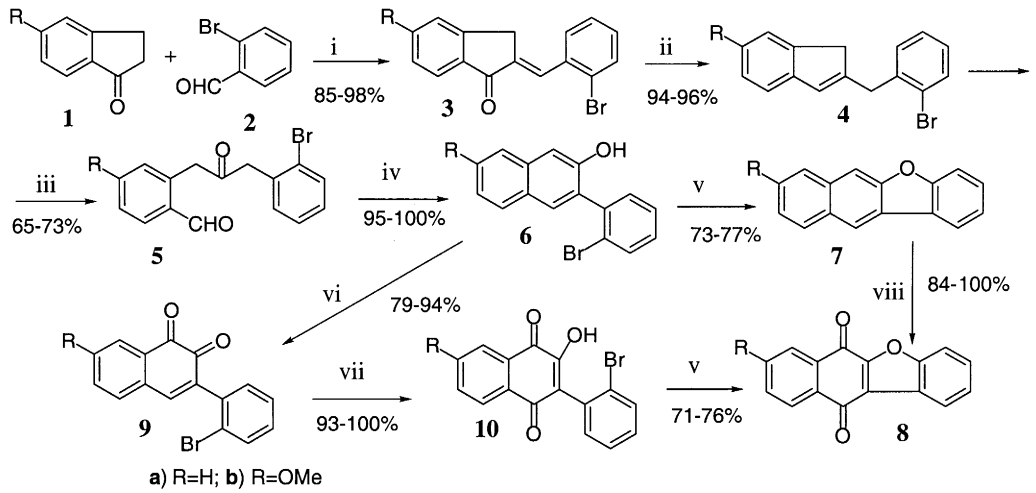

Scheme 1. Conditions. (i) NaMeO/MeOH, rt, 15–27 h; (ii) (a) H_2, Pd/C, AcOEt, 1 atm, 75–210 min; (b) $NaBH_4$, MeOH, rt, 60–90 min; (c) H_2SO_4, reflux, 1–2 h; (iii) (a) O_3, −78°C, 3–6 min (b) Me_2S, −78°C (4–7 h), rt (13 h); (iv) NaOH aq., rt, 1.5–2 h; (v) CuO, K_2CO_3, pyr, reflux, 1.5–4 h (vi) Fremy's salt, K_2HPO_4, acetone, rt, 1–4 h; (vii) H_2SO_4, MeOH, reflux, 29 h; (viii) CrO_3, AcOH, reflux, 10 min

The potential of this new synthetic route was confirmed by the successful preparation of benzonaphthofuran **7b** and benzofuronaphthoquinone **8b** from 5-methoxyindanone **1b** via 2-(2′-oxo-3′-phenylpropyl)benzaldehyde **5b**.

To sum up, we have developed a general synthesis of benzonaphthofurans **7** and benzofuronaphthoquinones **8**, which is simpler and more efficient than previous syntheses, and which may have great utility as a new simple route to 2-naphthols, naphthoquinones and other potential derivatives of 2-(2′-oxo-3′-propyl)benzaldehydes **5**. A systematic study of the chemistry of compounds **5**, including optimization of the new route to benzofuronaphthoquinones **8** and preparation of similar naphthoquinone compounds, including indolenaphthoquinones, benzofluorenenaphthoquinones, is now in progress.

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5. All new compounds gave satisfactory analytical and spectroscopic data. Selected physical and spectroscopic data for **Compound 5a**: mp, 68–69°C (methanol); IR (ν, cm^{-1}, KBr), 1719 and 1693 (C=O); ^1H NMR (δ, ppm), 10.01 (s, 1H, HC=O), 7.56 (t, 1H, J=1.8 Hz, Ar-H), 7.53–7.24 (m, 7H, 7×Ar-H), 4.20 (s, 2H, -CH_2-) and 4.11 (s, 2H,-CH_2-). MS, *m/z*

(%), 318, 316 (M^+, 1), 237 (9), 147 (100). **Compound 5b**: mp, 87–88°C (methanol); IR (ν, cm^{-1}, KBr), 1723 and 1684 (C=O); ^1H NMR (δ, ppm), 9.76 (s, 1H, HC=O), 7.61 (d, J=8.5 Hz, 1H, Ar-H), 7.47 (d, J=7.9 Hz, 1H, Ar-H), 7.24–7.16 (m, 3H, 3×Ar-H), 6.83 (dd, J=8.5 Hz and J=2.3 Hz, 1H, Ar-H), 6.62 (d, J=2.3 Hz, 1H, Ar-H), 4.01 (s, 2H, -CH_2-), 4.00 (s, 2H, -CH_2-) and 3.75 (s, 3H, -OCH_3). MS, *m/z* (%), 348, 346 (M^+, 1), 267 (9), 149 (100). **Compound 7a**: mp, 210–212°C (methanol); IR (ν, cm^{-1}, KBr), 1100 (C-O-C); ^1H NMR (δ, ppm), 8.42 (s, 1H, Ar-H), 8.07–7.96 (m, 3H, 3×Ar-H), 7.93 (s, 1H, Ar-H) and 7.58–7.35 (m, 5H, 5×Ar-H); MS, *m/z* (%), 218 (M^+, 100). **Compound 7b**: mp, 208–210°C (methanol); IR (ν, cm^{-1}, KBr), 1222 (C-O-C); ^1H NMR (δ, ppm), 8.30 (s, 1H, Ar-H), 8.01 (d, J=7.6 Hz, 1H, Ar-H), 7.90 (d, J=7.6 Hz, 1H, Ar-H), 7.79 (s, 1H, Ar-H), 7.56–7.43 (m, 2H, 2×Ar-H), 7.34 (t, J=7.3 Hz, 1H, Ar-H), 7.24 (d, J=5.5 Hz, 1H, Ar-H), 7.14 (dd, J=9.0 Hz and J=2.4 Hz, 1H, Ar-H) and 3.96 (s, 3H, -OCH_3); MS, *m/z* (%), 248 (M^+, 93), 205 (100). **Compound 8a**: mp, 245–247°C (methanol); IR (ν, cm^{-1}, KBr), 1674 (C=O); ^1H NMR (δ, ppm), 8.34–8.22 (m, 3H, 3×Ar-H) and 7.81–7.48 (m, 5H, 5×Ar-H); MS, *m/z* (%), 248 (M^+, 100). **Compound 8b**: mp, 254–256°C (methanol); IR (ν, cm^{-1}, KBr), 1679 (C=O); ^1H NMR (δ, ppm), 8, 32 (d, J=7.5 Hz, 1H, Ar-H), 8.18 (d, J=8.6 Hz, 1H, Ar-H), 7.71–7.68 (m, 2H, 2×Ar-H), 7.61–7.50 (m, 2H, 2×Ar-H), 7.23 (s, 1H, Ar-H) and 4.00 (s, 3H, -OCH_3); MS, *m/z* (%), 248 (M^+, 3), 58 (100).