One-Pot Synthesis of 2*H*-Chromene Derivatives from *ortho*-Naphthoquinones

Fernando de C. da Silva,[a] Alessandra Jorqueira,[a] R. M. Gouvêa,[a] Maria C. B. V. de Souza,[a] R. Alan Howie,[b] James L. Wardell,[a] Solange M. S. V. Wardell,[c] Vitor F. Ferreira*[a]

[a] Universidade Federal Fluminense, Instituto de Química, Departamento de Química Orgânica, 24020-150 Niterói, Rio de Janeiro, Brazil

[b] Department of Chemistry, University of Aberdeen, Old Aberdeen, AB24 3EU, Scotland, UK

[c] Complexo Tecnológico, Medicamentos Farmanguinhos, Av. Comandante Guaranys 447, Jacarepaguá, Rio de Janeiro, RJ, Brazil
E-mail: cegvito@vm.uff.br

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Abstract: A general one-pot synthesis for 2*H*-chromenes is reported from *ortho*-naphthoquinones and allyltriphenylphosphonium salts, $[(RMeC{=}CHCH_2)Ph_3P]^+Br^-$, in the presence of aqueous NaOH and chloroform at room temperature.

Key words: chromenes, Wittig reaction, one-pot cyclisation, naphthoquinones

The chromene or benzopyran substructure is frequently found in naturally occurring heterocyclic compounds, many of which exhibit biological activity (Figure 1),[1] an example being naphthohydroquinone of the benzochromene type **1** isolated from the root of *Pentas bussei*[2] (Figure 1). The chromenes have been identified as apoptosis-inducing agents,[3] anti-HIV[4] and antibacterials.[5]

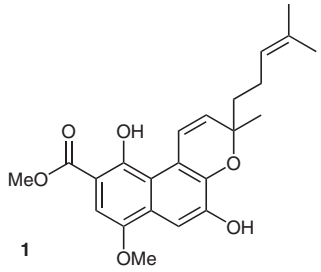
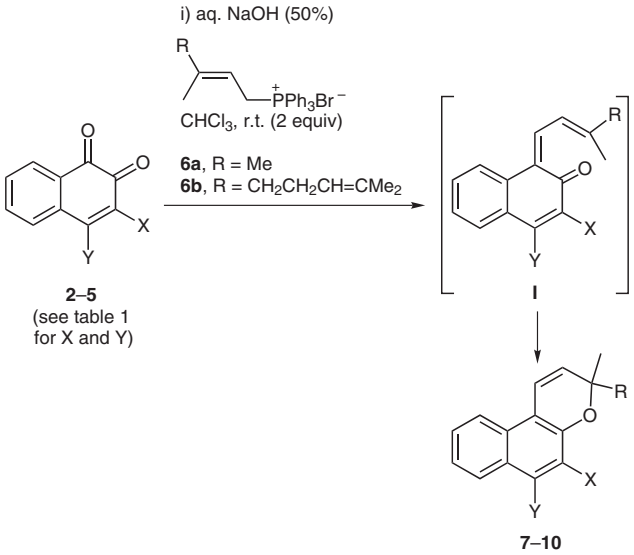


Figure 1 Structure of a compound isolated from the root of *Pentas bussei*

The chromenes have motivated a number of different synthetic approaches.[6–10] However, one-pot cyclisation routes to chromenes are not common.

Our general methodology involves the reactions of *ortho*-naphthoquinones **2–5** with two equivalents of an allyltriphenylphosphonium salt, $[(RMeC{=}CHCH_2)Ph_3P]^+Br^-$ (**6a** and **6b**), in the presence of aqueous NaOH solution (50%) and chloroform. The *ortho*-naphthoquinones used were *ortho*-naphthoquinones **2a**,**b**,[11] β-lapachone derivatives **3a–c**,[12] nor-β-lapachone (**4**)[13] and tetrachloro[1,2]benzoquinone (**5**; commercially available) (Table 1). The reaction proceeds via in situ formation of an ylide, $(Ph_3P{=}CH^-CH{=}CMeR)$, and its subsequent reaction with an *ortho*-naphthoquinone to produce a quinone methide intermediate **I**, which cyclises to a 2*H*-chromene, as outlined in Scheme 1. The yields ranging from 47% to 85% were the result of attack of the phosphorus ylide at the more reactive 1- or α-position carbonyl carbon of the *ortho*-naphthoquinone. No products were detected from attack at the 2- or β-carbonyl.



Scheme 1 Reaction of *ortho*-naphthoquinones with allyltriphenylphosphonium salts **5a** and **5b**

All chromene derivatives were characterized by spectroscopic means, e.g., by 1D and 2D ^1H and ^{13}C NMR techniques [$^1H \times {}^1H$-COSY, HETCOR ($^1H \times {}^{13}C$, $^1J_{CH}$)]. Specifically, the regiochemistry assigned to **7a** was confirmed by a comparison of its ^1H NMR spectrum with that of the isomeric derivative **11**, also known as lapachenole, produced by Snieckus et al.[14] using a different synthetic route. There was a clear difference in the ^1H NMR spectra

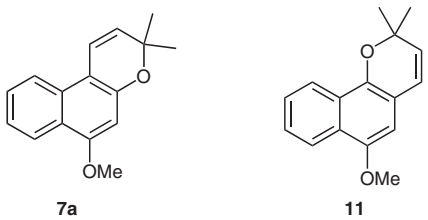


Figure 2 Structure of chromene **7a** and lapachenole (**11**)

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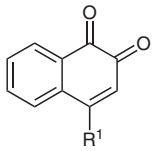
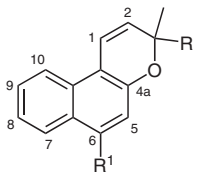
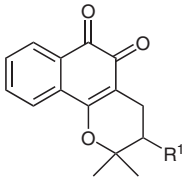
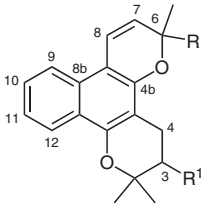
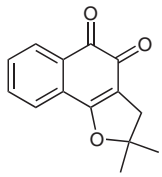
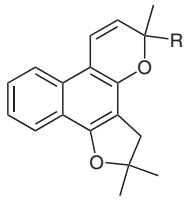
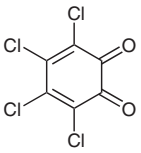
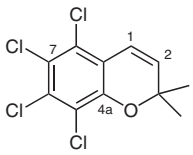
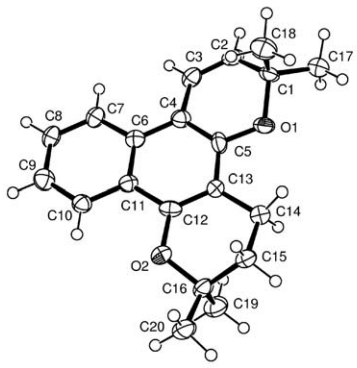
Table 1 Reactants, Products and Yields of the Reactions

Reactant		Product		Yield (%)
	**2a**: R^1 = OMe **2b**: R^1 = OEt		**7a**: R = Me, R^1 = OMe **7b**: R = $CH_2CH_2CH{=}CMe_2$, R^1 = OMe **7c**: R = Me, R^1 = OEt **7d**: R = $CH_2CH_2CH{=}CMe_2$, R^1 = OEt	60 57 65 47
	**3a**: R^1 = H **3b**: R^1 = OH **3c**: R^1 = Br		**8a**: R = Me, R^1 = H **8b**: R = $CH_2CH_2CH{=}CMe_2$, R^1 = H **8c**: R = Me, R^1 = OH **8d**: R = $CH_2CH_2CH{=}CMe_2$, R^1 = OH **8e**: R = Me, R^1 = Br **8f**: R = $CH_2CH_2CH{=}CMe_2$, R^1 = Br	85 60 65 50 70 65
	**4**		**9a**: R = Me **9b**: R = $CH_2CH_2CH{=}CMe_2$	79 65
	**5**		**10**	40

of the two compounds, **7a** and **11** (Figure 2). Confirmation of the structure of lapachenole (**11**) had been further achieved by X-ray crystallography.[15] The products **8d** and **8f** were obtained as diastereoisomers but were not separated.

The structure of **8a** was confirmed by X-ray crystallography.[16–18] Figure 3 shows the atomic arrangements and selected geometric parameters for **8a**. Despite the low refinement, the bond lengths and hydrogen positions in the newly formed pyran ring, led to an unambiguous conclusion that the ylide had attacked the C1-carbonyl carbon.



O(1)-C(5)	1.359(6)
O(1)-C(1)	1.459(6)
C(1)-C(2)	1.499(8)
C(2)-C(3)	1.323(8)
C(3)-C(4)	1.457(8)
C(4)-C(5)	1.393(7)
C(1)-C(17)	1.514(8)
C(1)-C(18)	1.539(8)
C(5)-O(1)-C(1)	117.5(4)
O(1)-C(1)-C(2)	110.2(5)
C(3)-C(2)-C(1)	119.1(6)
C(2)-C(3)-C(4)	121.3(6)
C(5)-C(4)-C(3)	116.4(6)
O(1)-C(5)-C(4)	121.2(6)

Figure 3 Atom arrangement and selected bond angles (°) and lengths (Å) for **8a**

The chromene derivatives from β-lapachone (**3a**) and nor-β-lapachone (**4**) are of particular interest. β-Lapachones have significant biological activities. For example, **3a**, which is found in the heartwood of *Tabebuia sp.*, is effective in micromolar concentrations against a variety of cancer cells.[19] In addition, **3a** produces a diversity of pharmacological effects,[20] including antibacterial, antifungal, and trypanocidal activities. Many of their derivatives also have been found to have pharmacological properties.[21]

In summary, we have discovered a facile and general one-pot synthesis of 2*H*-chromenes[22] from *ortho*-naphthoquinones and allyltriphenylphosphonium salts, in the presence of aqueous NaOH and chloroform at room temperature.

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(18) Crystal data collected at 120 K, colourless crystal: 0.16 × 0.10 × 0.06 mm^3. Formula: $C_{20}H_{22}O_2$; M = 294.38; monoclinic, *P*21/*c*, *a* = 8.657(2) Å, *b* = 7.9525(17) Å, *c* = 23.385(6) Å, *β* = 92.815(9)°, *Z* = 4, *V* = 1608.0(7) Å^3, 3696 independent reflections [*R*(int) = 0.1482], 1562 observed reflections [I >2s(I)]; parameters refined: 203; number of restraints: 0; *R*(F): 0.1839 (obs. data), $\Delta\rho_{max}$ = 0.28 Å^{-3}. CCDC deposition no: 292382.

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(22) **General Procedure for 2*H*-Chromenes 7–10**: A mixture of the naphthoquinone (0.02 mol), allyltriphenylphosphonium salt (0.04 mol), $CHCl_3$ (15 mL) and aq 50% NaOH (15 mL, 0.19 mol) was vigorously stirred for 48 h at r.t. The organic phase was collected, washed with H_2O (3 × 10 mL), dried over $MgSO_4$ and the solvent was evaporated. Purification of the crude product was achieved by flash column chromatography using hexane–CH_2Cl_2 as eluent.
6-Methoxy-3,3-dimethyl-3*H*-benzo[*f*]chromene (7a): IR (KBr): 2971, 2938, 1634, 1588, 1574, 1515, 1464, 1450, 1443, 1411, 1379, 1351, 1283, 1247, 1220, 1207, 1199, 1160, 1130, 1119, 1092, 996, 981, 885, 841, 755, 727, 694, 626 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.50 (s, 6 H, Me), 3.98 (s, 3 H, OMe), 5.58 (d, *J* = 9.8 Hz, 1 H, H-2), 6.48 (s, 1 H, H-5), 6.95 (d, *J* = 9.8 Hz, 1 H, H-1), 7.30 (ddd, *J* = 1.2, 6.8, 8.5 Hz, 1 H, H-8), 7.49 (ddd, *J* = 1.2, 6.8, 8.3 Hz, 1 H, H-9), 7.89 (ddd, *J* = 0.7, 1.2, 8.3 Hz, 1 H, H-7), 8.17 (ddd, *J* = 0.7, 1.2, 8.5 Hz, 1 H, H-10). ^{13}C NMR (75.0 MHz, $CDCl_3$): δ = 27.4 (Me), 27.4 (Me), 55.5 (OMe), 76.2 (C-3), 97.4 (C-5), 106.8 (C-10b), 118.1 (C-1), 120.9 (C-10), 121.3 (C-6a), 122.3 (C-7), 122.5 (C-8), 126.0 (C-2), 127.1 (C-9), 130.4 (C-10a), 151.6 (C-4a), 156.4 (C-6). EIMS: *m*/*z* (%) = 240 (22) [M$^+$], 225 (100), 210 (15). HRMS: *m*/*z* calcd for $C_{16}H_{16}O_2$: 240.1150; found: 240.1139.
2,2,6,6-Tetramethyl-3,4-dihydro-2*H*,6*H*-1,5-dioxatriphenylene (8a): mp 89–90 °C. IR (KBr): 2975, 2934, 1637, 1578, 1510, 1465, 1453, 1428, 1418, 1396, 1383, 1369,

1360, 1325, 1289, 1253, 1237, 1220, 1195, 1159, 1137, 1119, 1003, 974, 881, 762, 732, 710, 691, 665, 646 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 6 H, Me), 1.47 (s, 6 H, Me), 1.86 (t, *J* = 6.8 Hz, 2 H, H-3), 2.77 (t, *J* = 6.8 Hz, 2 H, H-4), 5.54 (d, *J* = 10.0 Hz, 1 H, H-7), 6.95 (d, *J* = 10.0 Hz, 1 H, H-8), 7.27 (ddd, *J* = 1.2, 6.8, 8.3 Hz, 1 H, H-11), 7.41 (ddd, *J* = 1.2, 6.8, 8.3 Hz, 1 H, H-10), 7.85 (ddd, *J* = 0.5, 1.2, 8.3 Hz, 1 H, H-12), 8.14 (ddd, *J* = 0.5, 1.2, 8.3 Hz, 1 H, H-9). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.9 (C-4), 29.3 (Me), 29.3 (Me), 78.6 (C-6), 34.7 (C-3), 77.1 (C-2), 78.6 (C-6), 106.6 (C-8a), 110.3 (C-4a), 121.2 (C-9), 123.3 (C-12), 123.6 (C-12a), 124.6 (C-11), 124.8 (C-8), 128.0 (C-7), 128.7 (C-10), 131.6 (C-8b), 152.5 (C-4b), 152.6 (C-13). EIMS: *m*/*z* (%) = 294 (44) [M^+], 279 (77), 223 (100). HRMS: *m*/*z* calcd for $C_{20}H_{22}O_2$: 294.1620; found: 294.1617.

5,6,7,8-Tetrachloro-2,2-dimethyl-2*H*-chromene (10): yellow solid; mp 83–84 °C. IR (KBr): 2924, 2870, 2854, 1681, 1600, 1455, 1428, 1392, 1379, 1327, 1308, 1237, 1225, 1205, 1151, 1051, 1018, 996, 970, 924, 900, 834, 791, 663 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.87 (d, *J* = 1.5 Hz, 3 H, Me), 1.88 (d, *J* = 1.5 Hz, 3 H, Me), 5.55 (dsept, *J* = 1.5, 8.3 Hz, 1 H, H-2), 6.92 (d, *J* = 8.3 Hz, 1 H, H-1). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.0 (Me), 26.4 (Me), 30.0 (C-3), 111.0 (C-1), 112.9 (C-5), 118.3 (C-2), 125.1 (C-8a), 126.0 (C-7), 128.0 (C-6), 144.9 (C-8), 146.7 (C-4a).