A New One-Pot Procedure for a Ring Contraction Reaction using Iodine/H_2O_2

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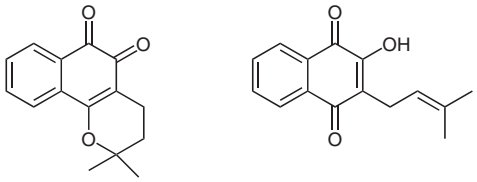
Abstract: A new procedure for ring contraction from 1,2-quinones using aqueous H_2O_2 (30%) and catalytic amount of I_2 in acetonitrile is reported.

Key words: ring contractions, quinones, lapachones, iodine, hydrogen peroxide

The cyclopentyl unit is present in several molecules, natural or non-natural, with remarkable biological activity. It can be found in alkaloids,[1a] steroids,[1b] prostaglandins,[1c] triquinanes,[1d] indans,[1e] and guaianes.[1f] Therefore, the development of efficient methods for the construction of such unit has been an important goal in organic synthesis. Probably, the most used strategies to prepare complex molecules possessing a functionalized cyclopentyl unit is by way of the cyclization reaction or by way of direct transformation of commercially available substrates that already contain this moiety. Although less used, the ring contraction of a carbocyclic compound is also a good route to assemble cyclopentyl units, because, in several cases, the reorganization of the bonds occurs with a high level of selectivity, leading to compounds not easily accessed by other methodologies.

Ring contraction reactions of carbocyclic compounds can be carried out by acids, bases, oxidizers and photochemically. The ring contraction reactions are divided into five main groups: (i) acid-induced ring contractions; (ii) base-induced ring contractions; (iii) oxidative rearrangements; (iv) photochemical rearrangements; and (v) Wolff rearrangements.[2] Since the transformation of carbocyclic compounds, particularly of quinones into different compounds, adds new biological applications possibilities,[3] it seems that an interesting starting point is to transform bioactive *o*-naphthoquinones, such as β-lapachone (**1**), into new compounds, like fluorenones.

Fluorenones can be prepared by intramolecular Friedel–Crafts acylations of biaryls.[4] The synthesis of fluorenones was reported by Snieckus and co-workers based on remote aromatic metalation[5] and, Chan and co-workers reported the synthesis of arenes by [3+3]-cyclization of 1,3-bissilyl enol ethers with 3-(silyloxy)alk-2-en-1-ones.[6] More recently, Langer and co-workers reported an efficient synthetic approach to fluorenones based on a '[3+3]-cyclization/Suzuki cross coupling/Friedel–Crafts acylation' strategy,[7] and recently, Mal and co-workers reported a two-step ring contraction of the generated benz[*a*]anthracene-5,6-diones through benzil–benzilic acid rearrangement for the preparation of the benzo[*b*] derivative.[8] Since 1996, several routes to the synthesis of fluorenones have been developed.[9]



1 2

Figure 1 Structure of lapachone (**1**) and its precursor lapachol (**2**), compound isolated from the lapacho tree

β-Lapachone (**1**) is a naturally occurring *o*-quinone derived from the lapacho tree (*Tabeuia avellanedae*) native to Central and South America. The synthesis and chemistry of β-lapachone and related compounds were initially investigated in the late 19th and early 20th centuries by the chemist Samuel Hooker,[10] and this compound is the most important one biogenetically related to lapachol (**2**; Figure 1).[11]

Fluorenone derivatives have been used in many polymers as electron-transporting materials in organic photoconductor devices and their electric and optical properties were studied. In addition, these moieties have remarkable medicinal interest since they can be found in natural compounds such as dengibsin (**3**), dendroflorin (**4**) or kinobscurinone (**5**), showing a range of interesting biological activities (Figure 2).[12a–c] However, only few reports are available for preparing such kind of compounds by short and direct synthetic procedures.

Iodine and H_2O_2 are environmentally safe and inexpensive reagents. The mixture of these reagents has been used in several organic reactions. For example, Stavber et al. found that the reaction using elemental iodine, enhanced by 30% aqueous hydrogen peroxide in water with ketones, 1,3-dicarbonyl derivatives and activated aromatic molecules gave an efficient iodofunctionalization.[13] Recently, Zÿmitek and co-worker used these reagents with different ketones that were directly converted into the corresponding *gem*-dihydroperoxides.[14]

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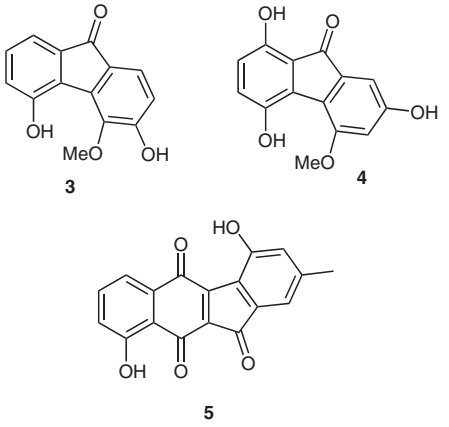
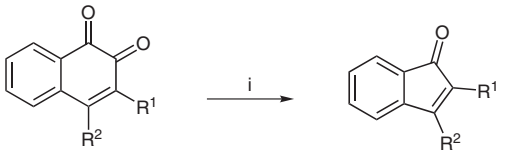


Figure 2 Structures of different fluorenone derivatives



(See Table 1 for R^1 and R^2)

Scheme 1 General scheme of the reaction of *o*-quinones with I_2–H_2O_2. *Reagents and conditions*: (i) 30% aq H_2O_2, I_2, MeCN, r.t.

In this communication we report a new approach to perform ring contraction in one-pot procedure from *o*-naphthoquinones in aqueous H_2O_2 (30%) and catalytic amount of iodine in acetonitrile (Scheme 1).

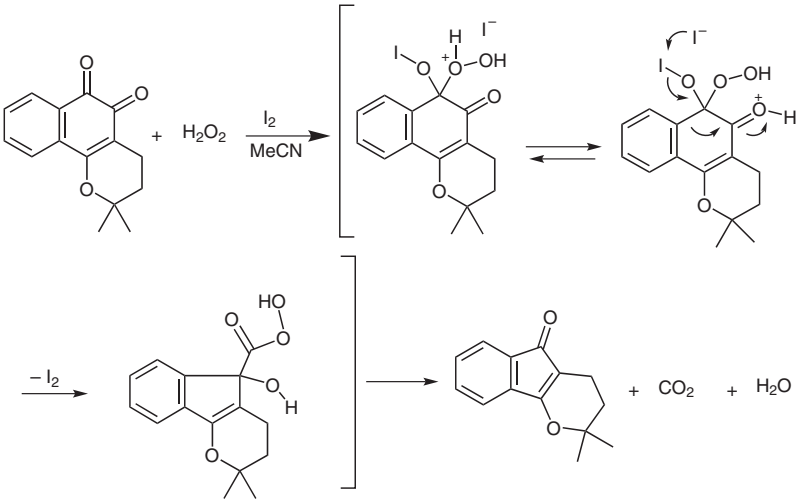
Since iodine has proven to be a useful Lewis acid catalyst for the activation of carbonyl compounds, including acetalization reactions,[15] it seems that the molecular iodine would activate one of the carbonyl carbons before H_2O_2 addition (Scheme 2).

Then, using these reagents, the fluorenones derivatives **18–24** were obtained in high yield from several *o*-naphthoquinones (Table 1, entries 1–4). The amount of I_2 was catalytic and the reaction time varied according the *o*-quinones. An increase in the amount of H_2O_2 and an extended reaction time did not bring about any further improvement in yield. The best results for the synthesis of products were achieved using a 0.1 M solution of *o*-naphthoquinone in acetonitrile, four equivalents of 30% aqueous H_2O_2, and 10 mol% of I_2 at room temperature.

To determine the limitations of the method, we tested the efficiency of this transformation with other types of *o*-quinones (Table 1, entries 5 and 6), all of which worked very well. However, this reaction was found to be limited to *o*-quinones, since *p*-quinones (entries 7 and 8) did not produce the expected ring contraction products even at higher catalyst concentrations and one week reaction time.

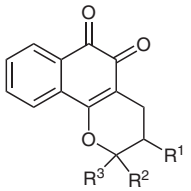
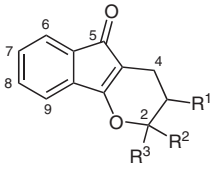
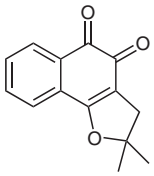
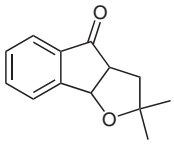
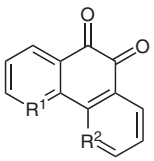
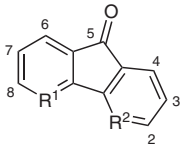
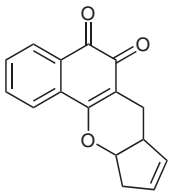
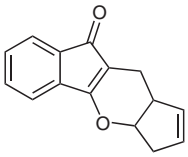
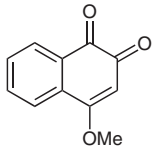
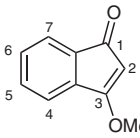
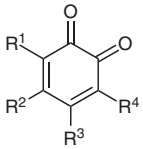
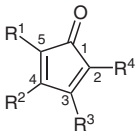
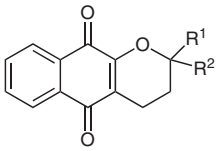
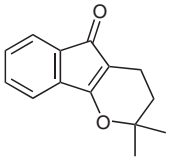
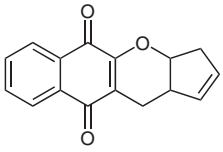
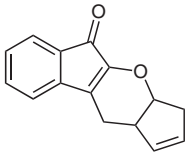
All derivatives were characterized by spectroscopic means, e.g., by 1D and 2D ^1H and ^{13}C NMR techniques (including COSY, HMBC and HMQC). The structures of compounds **22** and **23** were confirmed by the comparison of their spectra with those reported in literature, produced by a different synthetic route.[16a]

Specifically, the $^1H \times ^{13}C$ NMR spectrum was used to confirm the disappearance of one carbonyl signal and the coupling of H-4 and C5, for example, in product **18**. To our knowledge, this ring contraction directly from β-lapachone has not been reported previously. However, **18** was obtained by Chan and co-workers[17] as the major blood metabolite of β-lapachone (**1**), also known as ARQ501, a promising anticancer agent that is currently in multiple phase II clinical trials. In this regard, the present iodine–hydrogen peroxide reaction reproduces the same ring-contraction product formed by biotransformation of **1**. In view of the easy transformation of β-lapachone (**1**) to **18** in the I_2–H_2O_2 system, as well as in the human blood, and knowing that it interacts with P450 reductase, producing reactive species, superoxide anion radical,[18] we speculate that there may be a relationship between production of hydrogen peroxide by **1** and its biochemical degradation.



Scheme 2 Proposed mechanism for the ring contraction

Table 1 Reactants, Time, Products and Yields of the Reactions

Entry	Reactant		Time (h)	Product		Yield (%)[a]
1		**1**: R^1 = H; R^2 = R^3 = Me **6**: R^1 = Br; R^2 = R^3 = Me **7**: R^1 = R^2 = H; R^3 = Ph	24 24 24		**18**: R^1 = H; R^2 = R^3 = Me **19**: R^1 = Br; R^2 = R^3 = Me **20**: R^1 = R^2 = H; R^3 = Ph	87 75 90
2		**8**	24		**21**	90
3		**9**: R^1 = R^2 = N **10**: R^1 = R^2 = C	48 48		**22**: R^1 = R^2 = N **23**: R^1 = R^2 = C	65 88
4		**11**	24		**24**	89
5		**12**	24		**25**	76
6		**13**: R^1 = R_2 = R_3 = R_4 = Cl **14**: R^1 = R_3 = H; R^2 = R^4 = *t*-Bu	48 48		**26**: R^1 = R^2 = R^3 = R^4 = Cl **27**: R^1 = R^3 = H; R^2 = R^4 = *t*-Bu	78 75
7		**15**: R^1 = R^2 = Me **16**: R^1 = H; R^2 = Ph	One week One week		**28**	Not formed
8		**17**	One week		**29**	Not formed

[a] Yield after column chromatography.

In conclusion, iodine-catalyzed ring contraction of *o*-quinones with aqueous H_2O_2–I_2 in acetonitrile is a straightforward and efficient method for the synthesis of cyclopentyl units and fluorenone derivatives.[19]

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(19) **Preparation of 18; Representative Procedure for Ketones 18–27**: To a solution of I_2 (0.1 mmol, 25.4 mg) and 30% aq H_2O_2 (4 mmol, 0.45 mL) in MeCN (10 mL), β-lapachone (**1**; 1 mmol, 154 mg) was added and the solution was stirred at r.t. for 24 h. The reaction mixture was concentrated under reduced pressure and added to CH_2Cl_2 (10 mL). The organic phase was separated and washed with aqueous solution of sat. $Na_2S_2O_3$ (3 × 10 mL), dried over anhyd Na_2SO_4 and evaporated. The crude product was purified by flash column chromatography on silica gel using hexane–EtOAc as eluent.

2,2-Dimethyl-3,4-dihydro-2*H*-indeno[1,2-*b*]pyran-5-one (18): yellow solid; mp 54–56 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (s, 3 H, Me), 1.46 (s, 3 H, Me), 1.98–2.08 (m, 1 H, H-3a), 2.21–2.29 (m, 2 H, H-3b, H-4a), 2.95–3.04 (m, 1 H, H-4b), 7.82 (m, 2 H, H-9), 8.04 (ddd, *J* = 0.5, 1.2, 8.3 Hz, 1 H, H-6), 8.22 (ddd, *J* = 0.5, 1.2, 8.3 Hz, 1 H, H-9). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.5 (Me), 29.0 (Me), 32.6 (C-3), 36.4 (C-4), 88.2 (C-2), 110.0 (C-4a), 126.5 (C-9), 128.5 (C-9a), 130.1 (C6), 131.4 (C-6a), 134.1 (C-7), 134.9 (C8), 162.4 (C-9b), 187.2 (C=O). Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.28; H, 6.82.

5*H*-Cyclopenta[2,1-*b*:3,4-*b′*]dipyridin-5-one (22): pale yellow solid; mp 213–215 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36 (dd, *J* = 5.2, 7.3 Hz, 2 H, H-4, H-6), 7.98 (dd, *J* = 1.9, 7.3 Hz, 2 H, H-3, H-7), 8.78 (dd, *J* = 1.9, 5.2 Hz, 2 H, H-2, H-8). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 124.6 (C-3, C-7), 128.9 (C-4, C-6), 131.4 (C-4a, C-5a), 154.7 (C-2, C-8), 163.0 (C-8a, C8b), 188.5 (C=O). Anal. Calcd for $C_{11}H_6N_2O$: C, 72.52; H, 3.32; N, 15.38. 8.78. Found: C, 72.45; H, 3.30; N, 15.28.

3-Methoxy-1*H*-inden-1-one (25): pale yellow solid; mp 67–69 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.98 (s, 3 H, OMe), 5.58 (s, 1 H, H-2), 7.45 (m, 4 H, H-4, H-5, H-6, H-7). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.5 (OMe), 97.0 (C-2), 122.3 (C-4), 122.5 (C-5), 123.3 (C-3a), 127.0 (C-6), 130.1 (C-7a), 123.2 (C-7), 160.2 (C-3), 190.5 (C=O). Anal. Calcd for $C_{10}H_8O_2$: C, 74.99; H, 5.03. Found: C, 75.00; H, 5.00.

2,4-Di-*tert*-butylcyclopentadienone (27): yellow solid; mp 32–35 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.14 (s, 9 H, Me), 1.20 (s, 9 H, 3 × Me), 7.70 (s, 1 H, H-5), 6.40 (s, 1 H, H-3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.6 (Me), 28.9 (Me), 32.4 (C-*t*-B), 33.5 (C-*t*-Bu), 110.5 (C-5), 135.6 (C-3), 140.0 (C-2), 170.5 (C-4), 190.5 (C=O). Anal. Calcd for $C_{13}H_{20}O$: C, 80.44; H, 9.82. Found: C, 80.55; H, 9.90.

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