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Arylation of lawsone through BF_3-mediated coupling of its phenyliodonium ylide with activated arenes and aromatic aldehydes

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ABSTRACT

Phenyliodonium ylide of lawsone, activated by $BF_3{\cdot}Et_2O$, reacts with electron-rich arenes to afford the corresponding 2-aryl-3-hydroxy-1,4-naphthoquinones, in a coupling reaction without metal catalysts. The same type of products, in greater variety and higher yields, are obtained from the reaction of the $BF_3{\cdot}Et_2O$-activated ylide with aromatic aldehydes in a synthetically and mechanistically interesting deformylation reaction.

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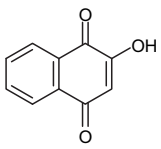
1. Introduction

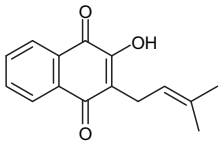
Aryliodonium ylides of hydroxyquinones offer an interesting example of compounds in which the chemistry of organic hypervalent iodine adds synthetic potentiality to an already important class: hydroxyquinones.

The term hydroxyquinones refers to quinones bearing at least one hydroxyl at the quinone moiety. A great number of them are found in nature,[1] in simple or more complicate structures, and their majority exhibits some kind of biological activity. Their chemistry has been reviewed some years ago.[2]

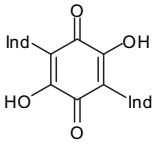
A few representative examples of naturally occurring hydroxyquinones in varying degrees of structure complexity are cited below.



1, Lawsone

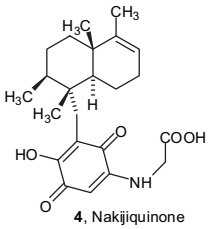


2, Lapachol

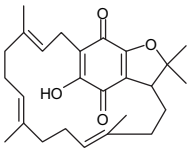


3. Asterriquinones

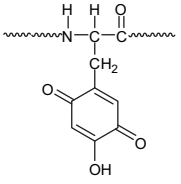
2-Hydroxy-1,4-naphthoquinone, lawsone (**1**), the main component of a natural hair dye, was also proved a potent detector of latent finger marks on cloth or paper under infrared light,[3] whereas its 3,3-dimethyl allyl derivative, lapachol (**2**), obtained from the homonymous tree, exhibits an impressive list of biological activities: *anti*-abscess, *anti*-ulcer, antileishmanial, anticarcinomic, antiedemic, *anti*-inflammatory, antimalarial, antiseptic, antitumor, antiviral, bactericidal, fungicidal, insectifugal, pesticidal, protisticidal, respiradepressant, schistosomicidal, termiticidal, and viricidal.[4] Bis-indolyl-dihydroxybenzoquinones, asterriquinones (**3**), exhibit a range of biological activities against cancer and diabetes,[5] while nakijiquinone (**4**) displays pronounced cytotoxicity against certain leukemia and carcinoma cells and acts as inhibitor of receptor tyrosine kinases, responsible for some types of cancer.[6] Tridentoquinone (**5**), the main pigment of an edible mushroom, exhibits an interesting structure and its biosynthesis was extensively studied,[7] and finally topaquinone (**6**), is the active site organic cofactor in copper-containing amine oxidases, which catalyze the enzymatic deamination of amines to aldehydes.[8]



4, Nakijiquinone



5, Tridentoquinone



6, Topaquinone

These few examples out of a great number of naturally occurring hydroxyquinones emphasize the importance of this class of

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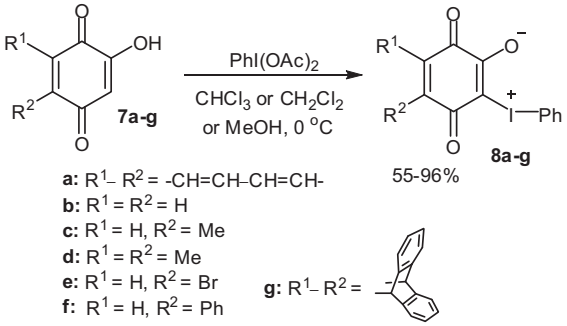
compounds. Their diverse chemistry is enriched with the involvement of hypervalent iodine chemistry: unsubstituted at the position next to hydroxy group hydroxyquinones form readily the corresponding zwitterionic iodonium compounds **8** (Scheme 1) upon reaction with diacetoxyiodobenzene (and other diacetoxyiodoarenes as well).[9]

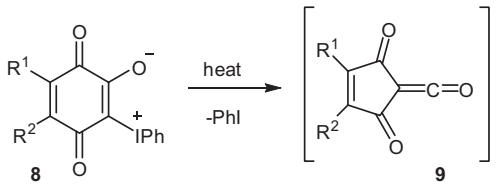


Scheme 1. Preparation of phenyliodonium ylides of hydroxyquinones.

These compounds are most conveniently isolated by filtration and can be stored for long periods without decomposition. Although their nature is rather zwitterionic, as indicated by the X-ray structure determination of **8a**[10] and an ^{127}I Mössbauer spectral study,[11] they are named as phenyliodonium ylides of the parent hydroxyquinone for simplicity reasons.

Regarding their reactivity two different patterns can be distinguished:

A. Upon refluxing suspensions of **8** in dichloromethane or acetonitrile the corresponding unstable α,α′-dioxoketenes **9** are produced through an iodobenzene elimination/Wolff rearrangement sequence (Scheme 2).



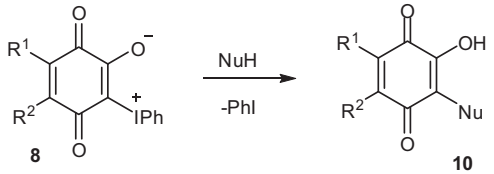
Scheme 2. Thermal decomposition of ylides to ketenes.

Initially it was thought that this ring contraction proceeds through the formation of carbenes but according to a recent DFT study[12] this transformation follows a single-step, transition-state concerted pathway with no intermediacy of carbenes. Moreover, ketene formation is kinetically and thermodynamically more favorable than aryl migration, observed in other cyclic aryliodonium analogs.

The non isolable ketenes **9** can be trapped with a variety of nucleophiles,[9] some of them leading to interesting enolic structures. In the absence of such agents, indanedione ketene, derived from the thermal decomposition of phenyliodonium ylide of lawsone **8a**, dimerizes to a labile spiro oxetanone derivative.[13] The latter reacts again with nucleophiles to afford in one or two steps a variety of indeno derivatives, some of which exhibit biological activity.[14]

B. The second reaction pathway is based on the activation of the position next to hydroxyl in parent hydroxyquinone by the aryliodonio group. Indeed, this easy-leaving group can be substituted by a variety of functional groups, mainly nucleophiles[9] (Scheme 3).

In this case the hydroxyquinone frame is retained and the reaction can afford naturally occurring hydroxyquinones or their analogs.

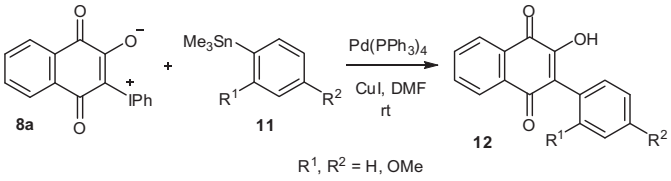


Scheme 3. Nucleophilic displacement of the phenyliodonio group.

Hydroxyquinones bearing an aryl (or heteroaryl) substituent at the position adjacent to hydroxyl (**10**, Nu=Ar) usually exhibit varying degrees of biological activity.[1,2,5] Hence, direct arylation of the hydroxyquinone ring is desirable. This arylation is effected by the reaction of the proper hydroxyquinone with aryldiazonium salts in alkaline solution, according to an older method,[15] but yields are generally low. In some cases nitroaryl groups can be coupled to hydroxyquinones using their fluoro–nitro derivatives in DMSO/K_2CO_3.[16]

The use of phenyliodonium ylides of hydroxyquinones facilitates the preparation of aryl-hydroxyquinones. Phenyliodonium ylide of 2-hydroxy-1,4-naphthoquinone **8a** reacts with indole derivatives to afford the corresponding indolyl-hydroxyquinones in the presence of catalytic amounts of Cu(II).[13]

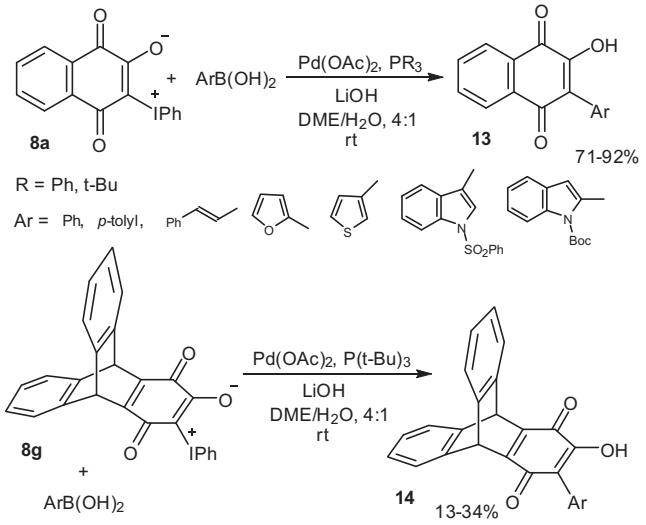
A more general methodology for the arylation of lawsone and its derivatives through their phenyliodonium ylides was suggested by Stagliano:[17] Stille-type coupling of ylide **8a** with arylstannanes **11** leads to **12** (Scheme 4).



Scheme 4. Stille-type coupling of ylide **8a** to aryl-hydroxyquinones.

Finally, we suggested recently the Suzuki-type coupling of **8a** with the more available and less toxic arylboronates.[18] The reaction takes place with a variety of aryl- and heteroarylboronates in DME/H_2O, giving fair to good yields of aryl lawsone derivatives **13** (Scheme 5).

The reaction takes place also with phenyliodonium ylides of other hydroxyquinones, such as that of hydroxy-triptycenoquinone



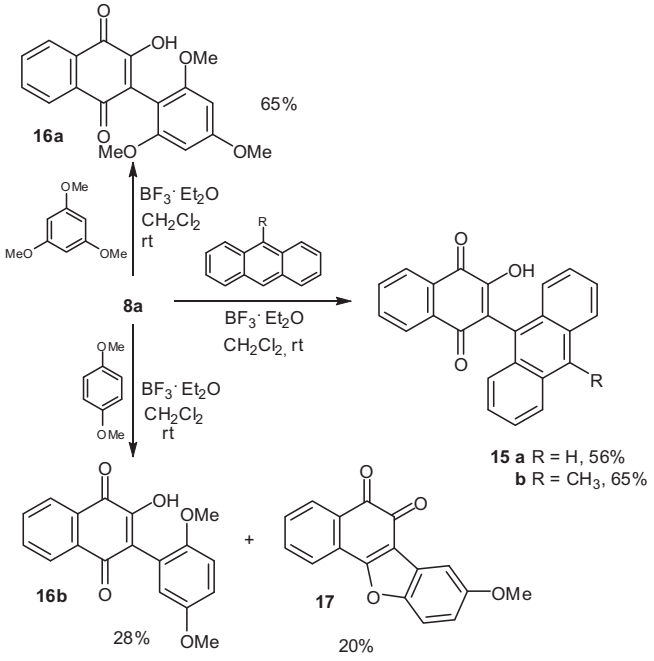
Scheme 5. Suzuki-type coupling of ylides **8a** and **8g** to aryl-hydroxyquinones.

8g, but the yields of the arylated products **14** are considerably lower.

Searching for a simpler method of transforming phenyliodonium ylides of hydroxyquinones to aryl-hydroxyquinones, we encountered Koser's paper describing the substitution reactions of electron rich aromatic compounds with BF_3-activated iodonium ylides of acyclic β-dicarbonyl compounds.[19] We tried an analogous methodology for ylide **8a** and report our findings here.

2. Results and discussion

Upon reaction of ylide **8a** with equimolecular amounts of anthracene and 9-methylanthracene and 2 equiv of $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at rt, the corresponding coupling products, hydroxyquinone derivatives **15a** and **15b**, were isolated in 56 and 65% yield, respectively (Scheme 6).



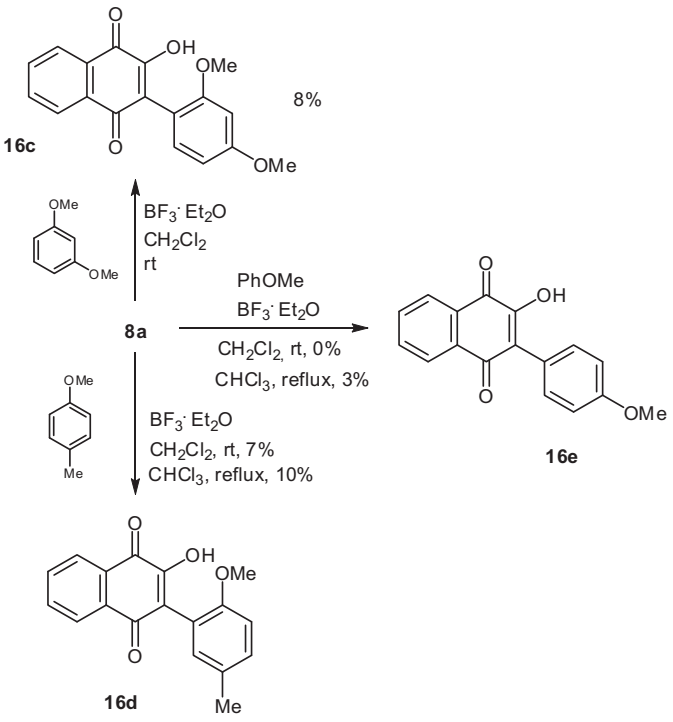
Scheme 6. $BF_3{\cdot}Et_2O$-mediated coupling of ylide **8a** with electron-rich arenes.

An analogous reaction with 1,3,5-trimethoxybenzene afforded 65% yield of hydroxyquinone **16a**, accompanied by varying small amounts of hexamethoxybiphenyl, whereas 1,4-dimethoxybenzene gave besides the expected coupling product **16b** (28%), the benzofurano-*o*-naphthoquinone derivative **17** in 20% yield. By conducting the same reaction in refluxing dichloromethane for 12 h, the respective yields were 46 and 9%.

The above results indicate that the yield of the reaction is not affected much by the temperature and depends on the reactivity of the arene. Indeed, the reaction of **8a** with 1,3-dimethoxybenzene afforded only 8% of the coupling product **16c**, and cresol methyl ether gave 7% of the corresponding quinone **16d** (Scheme 7). The yield of the latter was raised to 10% only after conducting the reaction in refluxing $CHCl_3$ for 30 h. Similarly, anisole did not react at all with **8a** in CH_2Cl_2 at rt, and coupling was possible in only 3% yield, only in refluxing $CHCl_3$ and after a prolonged reaction time (36 h).

Other arenes such as toluene, *p*-xylene, mesitylene, and durene did not afford coupling products with **8a**, at least at rt in dichloromethane, and that was the case with *N*,*N*-dimethyl-*p*-toluidine.

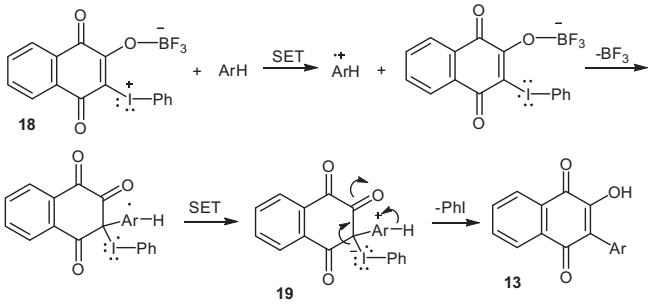
No coupling products were observed from the reaction, under the same conditions, of **8a** with activated heterocyclic rings such as



Scheme 7. $BF_3{\cdot}Et_2O$-mediated coupling of ylide **8a** with less electron-rich arenes.

furan, *N*-methylpyrrole, thiophene, 2-methylthiophene, and *N*-methylindole. In most cases, $BF_3{\cdot}Et_2O$ reacted with the heterocycle.

Regarding the reaction pathway of the coupling, it must be similar to the one proposed by Koser[19] for analogous couplings and based on the mechanism of PIFA oxidations of *p*-cresol ethers, extensively studied by Kita.[20] This mechanism is based on the assumption that the BF_3-complexed iodonium enolates (in our case **18**, Scheme 8) are stronger oxidants than the free ylides (in our case **8a**).

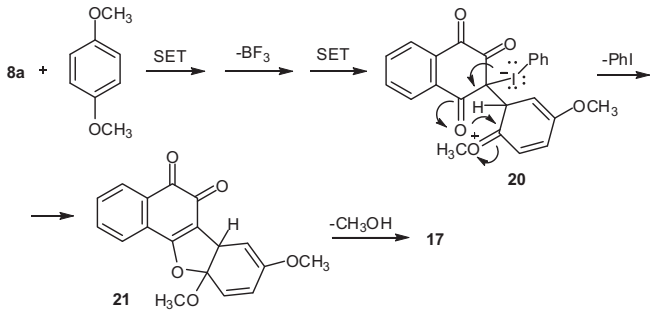


Scheme 8. Proposed reaction pathway.

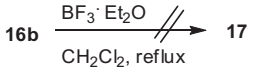
The so-formed complex **18** reacts with an electron-rich arene and through two single-electron-transfer (SET) steps affords the final coupling products **13**.

The same reaction pathway can explain the formation of the benzofurano-*o*-naphthoquinone derivative **17** from the reaction of 1,4-dimethoxybenzene with ylide **8a**: the intermediate **20**, analogous to **19**, formed by exactly the same sequence of reaction steps, in a parallel pathway can lead to **21**, which transforms to the final product **18** with loss of methanol (Scheme 9).

The assumption that **17** is formed during the main reaction pathway is verified by the fact that it was not possible to transform the coupling product **16b** to the fused **17**, in an independent reaction in the presence of $BF_3{\cdot}Et_2O$ in refluxing CH_2Cl_2 (Scheme 10).

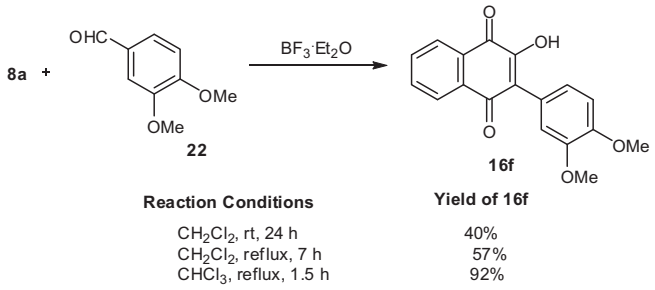


Scheme 9. Proposed reaction pathway for the formation of benzofurano-*o*-naphthoquinone **17**.



Scheme 10. The coupling product **16b** cannot be transformed to the fused **17**, in an independent reaction.

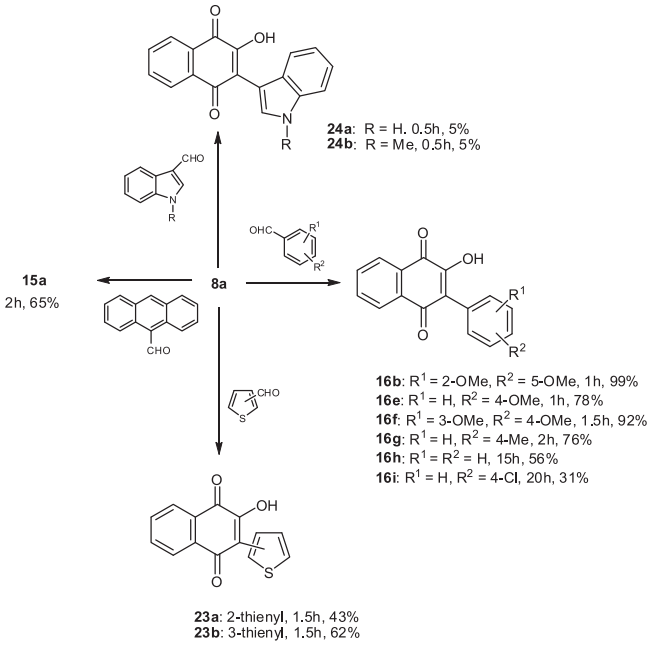
Regarding the level of activation of the arene, the above results show that at least two methoxy groups are necessary in order to obtain satisfactory yields of the coupling products. The presence of only one methoxy group in the aromatic ring, the case of anisole, is not enough for an effective electrophilic attack from the iodine of the ylide. Since two methoxy groups are sufficient for the coupling and one not, we tried the reaction of **8a** with 3,4-dimethoxybenzaldehyde (**22**), aiming to the partial deactivation of the aromatic ring by the electron-withdrawing formyl group. To our surprise, the coupling took place at the *ipso* carbon of the aldehyde with obvious loss of the formyl group, signaling a different kind of reactivity (Scheme 11). After some experimentation with conditions, the coupling product **16f** was isolated in 92% yield, using equimolecular quantities of ylide and $BF_3 \cdot Et_2O$ and a small excess (1:1.2) of aldehyde, in refluxing $CHCl_3$ for 1.5 h.



Scheme 11. Reaction conditions for the effective coupling of ylide **8a** with 3,4-dimethoxybenzaldehyde (**22**).

Similar conditions were applied for the reaction of **8a** with other aromatic aldehydes and the results are presented in Scheme 12. All the reactions were performed in dispersions of refluxing $CHCl_3$, till the occurrence of a clear solution. The time for the completion of each reaction and the yield of the coupling product appear on Scheme 12.

From the above results it is obvious that the coupling reaction of **8a** with aromatic aldehydes gives better yields than the corresponding with arenes. The results of the reaction with substituted benzaldehydes suggest that the richer in electrons the aromatic ring the higher the yield of the coupling products **16b**,**e**,**f**–**i** (and the shorter the reaction time). The reaction with anthracene-9-carbaldehyde affords the coupling product **15a** in 65% yield (compared to 56% yield of the same product resulting from the reaction with anthracene, Scheme 6).

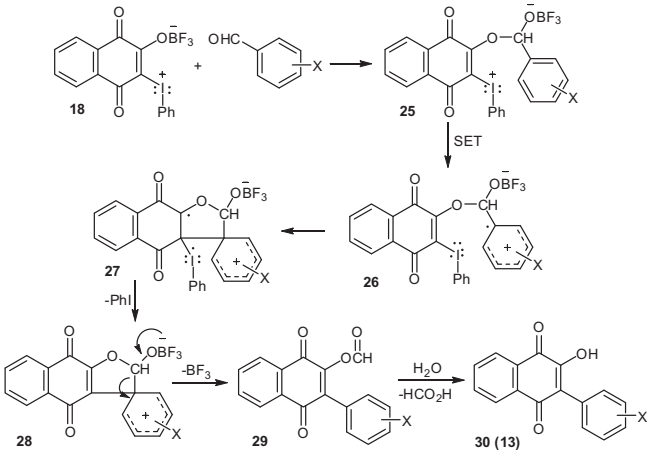


Scheme 12. Coupling reaction of ylide **8a** with aromatic aldehydes.

Although no coupling was observed from the reaction with heteroarenes, as it was mentioned earlier, some interesting results were obtained from the reaction with heteroaromatic aldehydes: thiophene-2- and 3-carbaldehydes afforded the corresponding coupling products **23a** and **23b** in 43 and 62% yield, respectively. It must be noted that, although compound **23b** was isolated from the Suzuki-type reaction of **8a** with thiophen-3-ylboronic acid, the **23a** isomer was never detected from the corresponding reaction with thiophen-2-ylboronic acid.[18]

Indole carbaldehydes afforded very low yields (5%) of the indolyl-hydroxynaphthoquinones **24a** and **24b**, perhaps suggesting that part of $BF_3 \cdot Et_2O$ binds to nitrogen, blocking the course of the reaction. This assumption may also explain the fact that no coupling took place between **8a** and pyrrole-2-carbaldehyde. The same was true for the reaction with furfural, where an extensive polymerization was observed.

Regarding the mechanism of the reaction it is obviously different from the corresponding of the reaction with arenes, suggested in Scheme 8. Here a coupling/deformylation sequence takes place. A plausible reaction mechanism explaining this sequence is presented in Scheme 13.



Scheme 13. Reaction mechanism of the $BF_3 \cdot Et_2O$-mediated coupling of phenyliodonium ylide of lawsone with aromatic aldehydes.

The initially formed ylide-BF_3 complex **18** reacts with aldehyde to the corresponding complex **25**, which through an intramolecular-type SET gives biradical **26**. The latter transforms to the coupled biradical **27**, which with loss of PhI and subsequent loss of BF_3 affords the ester **29** (1,4-dioxo-3-aryl-1,4-dihydronaphthalenyl-2-formate). Finally, formate **29** is hydrolyzed, probably during work-up on the chromatography column, to the desired arylated lawsone derivatives **30** (or **13** in more general presentation, Scheme 5). This reaction pathway seems plausible, although in the absence of solid evidence, an ionic mechanism, involving electrophilic addition of the aryliodonium group to the arene followed by ligand coupling, cannot be completely excluded.

This is an unusual hypervalent iodine and BF_3-mediated deformylation reaction that treats aldehydes as potential arylating agents. Decarbonylation of aldehydes is well known in organometallic chemistry and they are used as CO sources in Pauson/Khand-type reactions catalyzed by transition metals.[21]

3. Conclusions

As a conclusion we have described an easy, without the involvement of metal catalysts, coupling reaction between phenyliodonium ylide of lawsone (acting as a model compound) and both electron-rich arenes and aromatic aldehydes. Especially the latter reaction, being site selective and affording satisfactory to high yields of coupling products with a variety of aromatic aldehydes, might be the method of choice, for the preparation of aryl-hydroxyquinones. Since some biologically interesting compounds belong to this class of quinones, more targeted molecules can be accessed by application of this methodology, a task, that is, now in progress.

4. Experimental

4.1. General

Melting points were measured on a Kofler hot-stage and are uncorrected. NMR spectra were recorded at room temperature (rt) on a Bruker AM 300 spectrometer at 300 MHz for ^1H and 75 MHz for ^{13}C, using $CDCl_3$ as solvent. Chemical shifts are expressed in δ values (ppm) relative to TMS as internal standard for ^1H and relative to TMS (0.00 ppm) or to $CDCl_3$ (77.05 ppm) for ^{13}C NMR spectra. Coupling constants ^nJ are reported in Hertz. IR spectra were recorded on a Perkin–Elmer 1600 series FTIR spectrometer and are reported in wave numbers (cm^{-1}). The high resolution mass spectra were obtained at the facilities of the chemistry department of the University of Leipzig. Column chromatography was carried out using Merck silica gel. Petroleum ether refers to the fraction boiling between 60 and 80 °C. Phenyliodonium ylide of lawsone **8a** was prepared from lawsone and $PhI(OCOCH_3)_2$ according to the literature method.[22]

4.2. General procedure for the $BF_3\cdot Et_2O$-mediated coupling of phenyliodonium ylide of lawsone with arenes

A suspension of ylide **8a** (376 mg, 1.0 mmol), $BF_3\cdot Et_2O$ (0.26 mL, 2.0 mmol) and the proper arene (1.0 mmol) in CH_2Cl_2 (10 mL) was stirred overnight at rt. The resulting intensively colored suspension, after concentration was subjected to column chromatography (silica gel, petroleum ether/ethyl acetate 3:1, gradually increasing to 1:1) to afford the coupling products.

4.2.1. Reaction with anthracene.

*4.2.1.1. 2-(Anthracen-9-yl)-3-hydroxynaphthalene-1,4-dione (**15a**).* Compound **15a** as red crystals in 56% yield: mp 260–262 °C; IR (KBr) cm^{-1} 3363, 1652, 1632, 1589; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.54 (s, 1H), 8.26 (d, J=6.7 Hz, 1H), 8.21 (d, J=7.3 Hz, 1H), 8.05 (d, J=8.0 Hz, 2H), 7.86–7.73 (m, 4H), 7.49–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 183.8, 181.5, 154.7, 135.5 135.2 133.4, 131.4, 129.9, 129.8, 129.0, 128.4, 127.6, 126.6, 126.2, 125.4, 125.2; ESI-HRMS m/z calcd for $C_{24}H_{14}O_3$+H (MH^+) 351.10157, found 351.10146.

4.2.2. Reaction with 9-methylanthracene.

*4.2.2.1. 2-Hydroxy-3-(10-methylanthracen-9-yl)naphthalene-1,4-dione (**15b**).* Compound **15b** as red crystals in 65% yield: mp >280 °C; IR (KBr) cm^{-1} 3329, 1664, 1647, 1590; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.38 (d, J=8.8 Hz, 2H), 8.30 (d, J=7.3 Hz, 1H), 8.22 (d, J=7.3 Hz, 1H), 7.91–7.77 (m, 4H), 7.57–7.39 (m, 5H), 3.18 (s, 3H); ^{13}C NMR ($CDCl_3$+DMSO-d_6, 75 MHz) δ 183.6, 180.7, 156.2, 134.0 132.4 132.0, 129.9, 129.1, 128.8 128.4, 126.0, 125.8, 125.6 124.6, 124.3, 13.5; ESI-HRMS m/z calcd for $C_{25}H_{16}O_3$+Na (MNa^+) 387.09917, found 387.09916.

4.2.3. Reaction with 1,3,5-trimethoxybenzene.

*4.2.3.1. 2-Hydroxy-3-(2,4,6-trimethoxyphenyl)naphthalene-1,4-dione (**16a**).* Compound **16a** as yellow crystals in 65% yield: mp 257–260 °C; IR (KBr) cm^{-1} 3315, 1677, 1640, 1610; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.09 (2d, appearing as t, J=8.5 Hz, 2H), 7.76 (t, J=6.7 Hz, 1H), 7.69 (t, J=6.7 Hz, 1H), 7.32 (br s, 1H), 6.23 (s, 2H), 3.86 (s, 3H), 3.74 (s, 6H); ^{13}C NMR ($CDCl_3$+DMSO-d_6, 75 MHz) δ 182.6, 180.9, 161.0, 157.9, 154.6 133.4, 132.2, 131.8, 129.5, 125.6, 125.1, 117.4, 101.1, 90.1, 55.0, 54.5; ESI-HRMS m/z calcd for $C_{19}H_{16}O_6$+H (MH^+) 341.10196, found 341.10194.

4.2.4. Reaction with 1,4-dimethoxybenzene.

*4.2.4.1. 2-(2,5-Dimethoxyphenyl)-3-hydroxynaphthalene-1,4-dione (**16b**).* Compound **16b** as orange crystals in 28% yield: mp 173–176 °C; IR (KBr) cm^{-1} 3281, 1674, 1649, 1593; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.15 (d, J=7.3 Hz, 1H), 8.10 (d, J=7.3 Hz, 1H), 7.75 (t, J=7.3 Hz, 1H), 7.68 (t, J=7.3 Hz, 1H), 6.92 (s, 2H), 6,82 (s, 1H), 3.76 (s, 3H), 3.62 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 183.1, 181.5, 153.2, 153.0, 151.4, 135.0, 132.9, 129.4, 127.0, 126.1, 120.6, 120.2, 116.8, 115.1, 112.5, 56.4, 55.6; ESI-HRMS m/z calcd for $C_{18}H_{14}O_5$+H (MH^+) 311.09140, found 311.09128 and *8-methoxybenzo*[*d*]*naphtho*-[1,2-*b*]*furan*-5,6-*dione* (**17**) as red crystals in 20% yield: mp 209–211 °C; IR (KBr) cm^{-1} 1702, 1662, 1633, 1592; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.07 (d, J=7.3 Hz, 1H), 7.91 (t, J=7.3 Hz, 1H), 7.80 (t, J=7.3 Hz, 1H), 7.68 (t, J=7.3 Hz, 1H), 7.50 (t, J=7.3 Hz, 1H), 7.05 (s, 1H), 6,96 (d, J=7.3 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 180.3, 174.7, 162.2, 159.8, 156.7, 135.4, 130.8, 130.6, 129.5, 128.5, 123.1, 122.7, 116.8, 114.3, 96.6, 55.9; ESI-HRMS m/z calcd for $C_{17}H_{10}O_4$+Na (MNa^+) 301.04713, found 301.04731.

4.2.5. Reaction with 1,3-dimethoxybenzene.

*4.2.5.1. 2-(2,4-Dimethoxyphenyl)-3-hydroxynaphthalene-1,4-dione (**16c**).* Compound **16c** as yellow crystals in 8% yield: mp 230–232 °C; IR (KBr) cm^{-1} 3309, 1666, 1651, 1609; ^1H NMR ($CDCl_3$, 300 MHz) δ 10.10 (br s, 1H), 8.11 (d, J=7.3 Hz, 1H), 8.08 (d, J=6.7 Hz, 1H), 7.82–7.70 (m, 2H), 7.11 (d, J=8.5 Hz, 1H), 6.57 (d, J=8.5 Hz, 1H), 6.54 (s, 1H), 3.84 (s, 3H), 3.74 (s, 3H); ^{13}C NMR ($CDCl_3$+DMSO-d_6, 75 MHz) δ 182.3, 181.0, 160.3, 157.5, 154.2, 133.5, 131.9, 131.2, 129.4, 125.6, 125.0, 120.2, 112.2, 103.7, 97.8, 54.8, 54.5; ESI-HRMS m/z calcd for $C_{18}H_{14}O_5$+Na (MNa^+) 333.07334, found 333.07344.

4.2.6. Reaction with 1-methoxy-4-methylbenzene.

*4.2.6.1. 2-Hydroxy-3-(2-methoxy-5-methylphenyl)naphthalene-1,4-dione (**16d**).* Compound **16d** as yellow crystals in 7% yield: mp 146–148 °C; IR (KBr) cm^{-1} 3334, 1673, 1644, 1594; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.16 (two overlapping doublets, appearing as t, J=7.9 Hz, 2H), 7.89 (t, J=7.3 Hz, 1H), 7.72 (t, J=7.3 Hz, 1H), 7.46 (br s, 1H), 7.20 (d, J=8.5 Hz, 1H), 7.05 (s, 1H), 6.91 (d, J=8.5 Hz, 1H), 3.76 (s, 3H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 183.4, 181.8, 155.2, 152.8, 135.1, 133.1, 132.9, 131.7, 130.8, 129.7, 129.5, 127.2, 126.2, 119.1, 111.4, 55.9, 20.5; ESI-HRMS m/z calcd for $C_{18}H_{14}O_4$+H (MH^+) 295.09648, found 295.09641.

4.2.7. Reaction with methoxybenzene. The coupling product **16e** was not obtained after stirring overnight at rt, but it was isolated in only 3% yield when the reaction was performed in refluxing $CHCl_3$ for 36 h.

*4.2.7.1. 2-Hydroxy-3-(4-methoxyphenyl)naphthalene-1,4-dione (**16e**).* Compound **16e** as red crystals, mp 170–172 °C (lit.[17a] mp 172–173 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.18 (dd, J_1=7.8 Hz, J_2=1.2 Hz, 1H), 8.12 (dd, J_1=7.5 Hz, J_2=1.2 Hz, 1H), 7.78 (dt, J_1=7.8 Hz, J_2=1.2 Hz, 1H), 7.70 (dt, J_1=7.5 Hz, J_2=1.2 Hz, 1H), 7.62 (br s, 1H), 7.50 (d, J=9.0 Hz, 2H), 6.99 (d, J=9.0 Hz, 2H), 3.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 184.0, 181.8, 159.9, 151.9. 135.1, 133.1, 132.9, 132.2, 129.4, 127.2, 126.0, 122.2, 121.9, 113.5, 55.3.

4.3. General procedure for the $BF_3\cdot Et_2O$-mediated coupling of phenyliodonium ylide of lawsone with aromatic aldehydes

A suspension of ylide **8a** (188 mg, 0.5 mmol), $BF_3\cdot Et_2O$ (0.06 mL, 0.5 mmol) and the proper aromatic aldehyde (0.6 mmol) in $CHCl_3$ (10 mL) was refluxed till a clear solution results (0.5–20 h). The resulting intensively colored solution, after concentration was subjected to column chromatography (silica gel, petroleum ether/ethyl acetate 3:1, gradually increasing to 1:1), to afford the coupling products.

4.3.1. Reaction with 2,5-dimethoxybenzaldehyde.

*4.3.1.1. 2-(2,5-Dimethoxyphenyl)-3-hydroxynaphthalene-1,4-dione (**16b**).* Compound **16b** in 99% yield, in all respects identical with the one prepared from the reaction of **8a** with 1,4-dimethoxybenzene.

4.3.2. Reaction with 4-methoxybenzaldehyde.

*4.3.2.1. 2-Hydroxy-3-(4-methoxyphenyl)naphthalene-1,4-dione (**16e**).* Compound **16e** in 78% yield, in all respects identical with the one prepared from the reaction of **8a** with methoxybenzene.

4.3.3. Reaction with 3,4-dimethoxybenzaldehyde.

*4.3.3.1. 2-(3,4-Dimethoxyphenyl)-3-hydroxynaphthalene-1,4-dione (**16f**).* Compound **16f** as red crystals in 92% yield: mp 178–179 °C (lit.[15c] mp 180 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.19 (d, J=8.6 Hz, 1H), 8.13 (d, J=8.6 Hz, 1H), 7.84–7.69 (m, 2H), 7.68 (br s, 1H), 7.18 (dd, J_1=7.7 Hz, J_2=1.7, 1H), 7.10 (d, J=1.7 Hz, 1H), 6.97 (d, J=7.7 Hz, 1H), 3.93 (s, 3H), 3.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 184.0, 181.7, 151.9, 149.3, 148.3, 135.2, 133.1, 132.8, 129.3, 127.2, 126.1, 123.9, 122.3, 121.9, 113.9, 110.5, 55.9, 55.8.

4.3.4. Reaction with 4-methylbenzaldehyde.

*4.3.4.1. 2-Hydroxy-3-p-tolylnaphthalene-1,4-dione (**16g**).* Compound **16g** as yellow crystals in 76% yield: mp 166–167 °C (lit.[23] mp 168 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.19 (dd, J_1=7.7 Hz, J_2=1.2 Hz, 1H), 8.14 (dd, J_1=7.4 Hz, J_2=1.2 Hz, 1H), 7.79 (dt, J_1=7.4 Hz, J_2=1.5 Hz, 1H), 7.71 (dt, J_1=7.5 Hz, J_2=1.5 Hz, 1H), 7.55 (br s, 1H), 7.42 (d, J=8.4 Hz, 2H), 7.26 (d, J=8.1 Hz, 2H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 183.8, 181.9, 152.1, 138.7, 135.2, 133.1, 133.0, 130.6, 129.4, 128.7, 127.3, 127.0, 126.1, 122.3, 21.4.

4.3.5. Reaction with benzaldehyde.

*4.3.5.1. 2-Hydroxy-3-phenylnaphthalene-1,4-dione (**16h**).* Compound **16h** in 56% yield: mp 147–148 °C (lit.[22] mp 146 °C), and spectra identical with the ones reported in the literature.[24]

4.3.6. Reaction with 4-chlorobenzaldehyde.

*4.3.6.1. 2-(4-Chlorophenyl)-3-hydroxynaphthalene-1,4-dione (**16i**).* Compound **16i** as yellow crystals in 31% yield: mp 186–188 °C (lit.[15a] mp 187–188 °C). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.19 (dd, J_1=7.7 Hz, J_2=1.2 Hz, 1H), 8.15 (dd, J_1=7.5 Hz, J_2=1.2 Hz, 1H), 7.82 (dt, J_1=7.5 Hz, J_2=1.5 Hz, 1H), 7.74 (dt, J_1=7.5 Hz, J_2=1.2 Hz, 1H), 7.67 (br s, 1H), 7.48 (d, J=8.7 Hz, 2H), 7.42 (d, J=8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 183.5, 181.7, 152.3, 135.4, 134.7, 133.3, 132.8, 132.2, 129.8, 128.5, 128.2, 127.4, 126.3, 121.0.

4.3.7. Reaction with anthracene-9-carbaldehyde.

*4.3.7.1. 2-(Anthracen-9-yl)-3-hydroxynaphthalene-1,4-dione (**15a**).* Compound **15a** in 65% yield, in all respects identical with the one prepared from the reaction of **8a** with anthracene.

4.3.8. Reaction with thiophene-2-carbaldehyde.

*4.3.8.1. 2-Hydroxy-3-(thiophen-2-yl)naphthalene-1,4-dione (**23a**).* Compound **23a** as purple crystals in 43% yield: mp 134–137 °C; IR (KBr) cm^{-1} 3344, 1636, 1602, 1588; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.25 (br s, 1H), 8.21 (dd, J_1=3.9 Hz, J_2=0.9 Hz, 1H), 8.19 (dd, J_1=7.8 Hz, J_2=1.2 Hz, 1H), 8.09 (dd, J_1=7.5 Hz, J_2=1.2 Hz, 1H), 7.77 (dt, J_1=7.5 Hz, J_2=1.5 Hz, 1H), 7.69 (dt, J_1=7.5 Hz, J_2=1.5 Hz, 1H), 7.60 (dd, J_1=5.1 Hz, J_2=0.9 Hz, 1H), 7.18 (dd, J_1=3.9 Hz, J_2=5.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 183.7, 180.9, 171.2, 150.1, 135.2, 133.4, 132.7, 132.5, 131.1, 129.1, 127.5, 126.8, 126.1, 116.0; ESI-HRMS m/z calcd for $C_{14}H_8O_3S$+Na (MNa^+) 279.00917, found 279.00871.

4.3.9. Reaction with thiophene-3-carbaldehyde.

*4.3.9.1. 2-Hydroxy-3-(thiophen-3-yl)naphthalene-1,4-dione (**23b**).* Compound **23b** as purple crystals in 62% yield: mp 125–127 °C (lit.[18] mp 126–127 °C).

4.3.10. Reaction with 1H-indole-3-carbaldehyde.

*4.3.10.1. 2-Hydroxy-3-(1H-indol-3-yl)naphthalene-1,4-dione (**24a**).* Compound **24a** as purple crystals in 5% yield: mp 223–226 °C; IR (KBr) cm^{-1} 3385, 3342, 1655, 1626, 1587; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.76 (d, J_1=3.3 Hz, 1H), 9.20 (br s, 1H), 8.34 (s, 1H), 8.06–8.01 (m, 1H), 7.99–7.93 (m, 2H), 7.79–7.71 (m, 2H), 7.52–7.47 (m, 1H), 7.41–7.31 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 184.2, 181.4, 151.0, 136.0, 134.8, 134.4, 133.3, 133.1, 129.8, 128.5, 127.3, 126.4, 126.0, 122.6, 122.2, 120.5, 111.3, 106.0, 30.9; ESI-HRMS m/z calcd for $C_{18}H_{11}NO_3$+Na (MNa^+) 312.06311, found 312.06316.

4.3.11. Reaction with 1-methyl-1H-indole-3-carbaldehyde.

*4.3.11.1. 2-Hydroxy-3-(1-methyl-1H-indol-3-yl)naphthalene-1,4-dione (**24b**).* Compound **24b** as purple crystals in 5% yield: mp 238–241 °C (lit.[13] mp 236–240 °C).

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