Functionalized Hydroxyquinones through Suzuki-Type Coupling of Phenyliodonium Ylides of Hydroxyquinones with Arylboronic Acids

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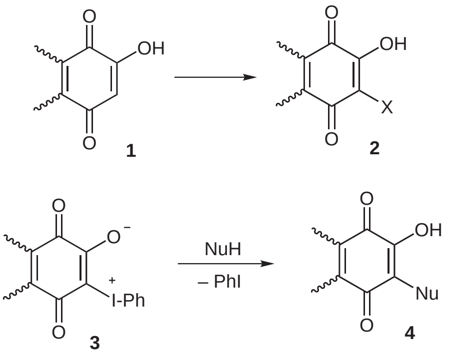
Dedicated to Prof. K. P. C. Vollhardt on the occasion of his 60th birthday.

Abstract: The palladium(II) acetate catalyzed reaction of phenyliodonium ylides of 2-hydroxyquinones with arylboronic acids affords a variety of 3-substituted 2-hydroxyquinone derivatives. Best yields are obtained by using tri(*tert*-butyl)phosphine as a ligand.

Key words: hydroxyquinones, phenyliodonium ylides, Suzuki coupling, palladium-catalyzed, boronic acids

Hydroxyquinones **1**, quinones bearing the hydroxyl on the quinone ring, constitute an interesting class of compounds as a great variety of them are found in nature with the majority exhibiting some kind of biological activity.[1] The chemistry of hydroxyquinones has been reviewed recently.[2]

An important feature of this chemistry is the functionalization of the position next to the hydroxyl group to obtain 3-substituted hydroxyquinones **2**. This functionalization can be achieved by different methodologies,[2] but a most effective one involves the use of phenyliodonium ylides **3**. The latter, most easily prepared from the corresponding hydroxyquinones **1** and diacetoxyiodobenzene,[3] react with a variety of nucleophiles to afford **4**, in an internal S_N2-type substitution reaction of the initially formed iodonium salt and reductive elimination of iodobenzene,[4] as illustrated in Scheme 1.

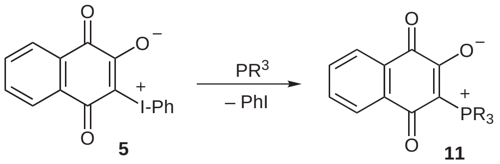


Scheme 1 Routes to 3-substituted-2-hydroxy-1,4-quinones.

Especially noteworthy are the C–C bond-forming reactions as a lot of hydroxyquinones bearing carbon substituents at position 3 exhibit intense biological activity, even if these substituents have a simple structure.[1,2]

A limited number of such transformations have been reported, the first being the photochemical reaction of the phenyliodonium ylide of lawsone (**5**) with alkenes and alkynes leading to dihydrofuro- and furonaphthoquinones respectively.[3a] The same ylide affords furonaphthoquinones in a Sonagashira-type coupling reaction with phenylacetylenes,[5] a reaction that proceeds also with Cu_2O, but only a few examples with low to medium yields have been reported. Stagliano developed a Stille-type coupling methodology involving arylstannanes and aryliodonium ylides of hydroxyquinones,[3c,d] on his way to preparing trimeric quinones analogous to conocurvone, a natural product and potential anti-HIV agent. Recently we reported[4] the copper-catalyzed coupling of phenyliodonium ylide of lawsone with indole derivatives to afford indolylquinones, a most interesting class of hydroxyquinones, related to the naturally occurring asterriquinones.[1,2]

Searching for a general methodology to access 3-aryl-substituted 2-hydroxyquinones, we investigated the palladium-catalyzed reaction of phenyliodonium ylides of hydroxyquinones under Suzuki-type coupling conditions and report our results herein. It must be noted that an analogous reaction with the phenyliodonium ylide of 4-hydroxycoumarin, leading to 3-aryl-4-hydroxycoumarins has been reported in the literature.[6]



Scheme 2 Transylidation side reaction.

In order to optimize the reaction conditions a series of experiments presented in Table 1 were conducted. The phenyliodonium ylide of lawsone (**5**) and 3-thienylboronic acid (**6a**) were selected as model compounds, on scales of 0.5 and 1.1 mmol, respectively. Reactions were carried out at room temperature in 10 mL of solvent (DME; DME–H_2O, 4:1; H_2O) under argon. Lithium hydroxide was used as a base and 4 mmol% of the appropriate palladium catalyst was added. Three different phosphine ligands, PPh_3, P(*c*-Hex)$_3$, and P(*t*-Bu)$_3$, were used with

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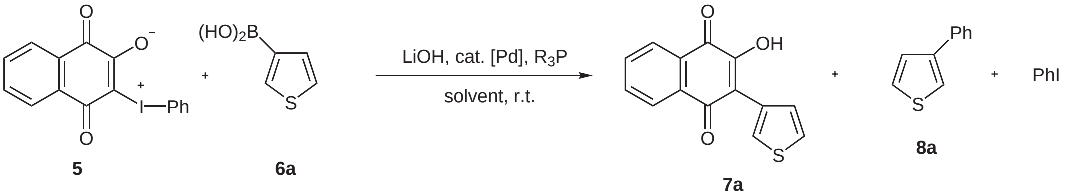
Table 1 Optimization of Conditions for the Coupling Reaction of Ylide **5** with 3-Thienylboronic Acid (**6a**)



Entry	Catalyst (4 mmol%)	Ligand	Solvent	Yield of **7a** (%)
1	$Pd(PPh_3)_2Cl_2$	–	$DME–H_2O$ (4:1)	18
2	$Pd(OAc)_2$	PPh_3	$DME–H_2O$ (4:1)	49
3	$Pd(OAc)_2$	PPh_3	DME	traces
4	$Pd(OAc)_2$	PPh_3	H_2O	32
5	$Pd(OAc)_2$	$P(c\text{-Hex})_3$	$DME–H_2O$ (4:1)	32
6	$Pd(OAc)_2$	$P(t\text{-Bu})_3$	$DME–H_2O$ (4:1)	92

$Pd(OAc)_2$ as a catalyst. Under these conditions the reaction was complete in five to eight hours, the resulting solution was acidified by the addition of acetic acid, extracted, and subjected to column chromatography.

The desired 2-hydroxy-3-(3-thienyl)-1,4-naphthoquinone (**7a**) was isolated in yields indicated in Table 1. It is obvious that the presence of water is necessary for the reaction and the best yields are obtained in $DME–H_2O$ (4:1). Another interesting feature of the reaction is that it can take place in water as the sole solvent, although the yield is lower. Finally, when $Pd(OAc)_2$ was used as a catalyst a spectacular increase in the yield of the substitution product **7a** was observed when $P(t\text{-Bu})_3$ was used as a ligand. This can be attributed to the increased steric hindrance of the latter, which minimizes the possibility of a transylidation reaction and the formation of the corresponding phosphonium ylide.[7]

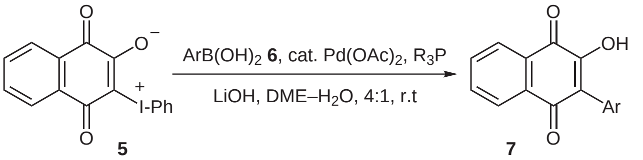
Iodobenzene (traces) was sometimes a side-product of the reaction as well as 3-phenylthiophene (**8a**) in yields analogous to the corresponding yields of **7a**. Phenylthiophene obviously resulted from the Suzuki coupling reaction of iodobenzene with excess thienylboronic acid necessary for the completion of the reaction.

The reaction of ylide **5** was repeated with different aryl- and heteroarylboronic acids under the optimum conditions with PPh_3 and $P(t\text{-Bu})_3$[8] (Table 2).

The results confirmed that the phosphine ligand affording the best yields was $P(t\text{-Bu})_3$ and that water was the optimum solvent,[9] although yields were lower in some cases.

The reaction of 2-thienylboronic acid (**6c**) with ylide **5** did not proceed under any conditions, not even in refluxing $DME–H_2O$. Judging by the fact that the reaction proceeded smoothly both with 3-thienylboronic acid (**6a**) and 2-furylboronic acid (**6d**), we assumed that some kind of stable complex is formed between the zwitterionic moiety of the ylide and the $SCB(OH)_2$ group of **6c**.

Table 2 Coupling Reaction of the Phenyliodonium Ylide of Lawsone with Arylboronic Acids



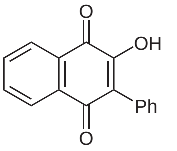
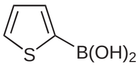
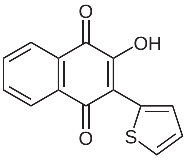
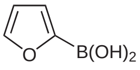
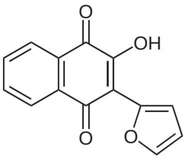
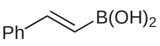
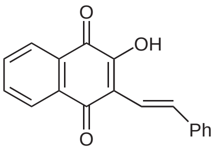
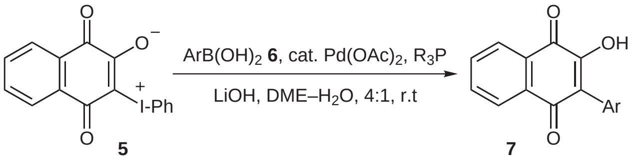
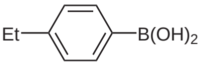
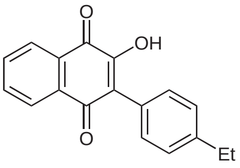
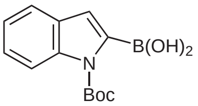
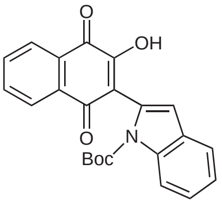
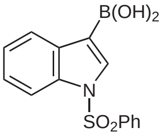
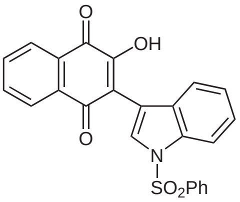
$ArB(OH)_2$	Coupling product	Yield (%) (PPh_3)	Yield (%) [$P(t\text{-Bu})_3$]
$PhB(OH)_2$ **6b**	 **7b**	72 (38)[a]	92 (89)[a]
 **6c**	 **7c**	0	0
 **6d**	 **7d**	36 (20)	77
 **6e**	 **7e**	28 (34)[a]	87

Table 2 Coupling Reaction of the Phenyliodonium Ylide of Lawsone with Arylboronic Acids (continued)



$ArB(OH)_2$	Coupling product	Yield (%) (PPh_3)	Yield (%) [P(*t*-Bu)$_3$]
 **6f**	 **7f**	19 (42)[a]	71
 **6g**	 **7g**	17	88
 **6h**	 **7h**	traces	88

[a] Yields in parentheses refer to H_2O as solvent.

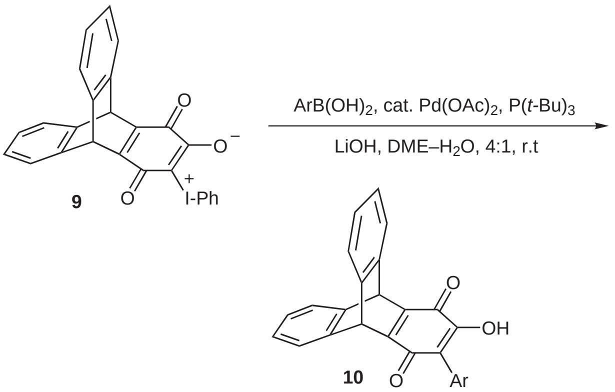
The high yield of the coupling product in the reaction of **5** with styrylboronic acid (**6e**) shows that the corresponding 3-alkenyl derivatives can also be prepared by the reported method. This finding is interesting as 3-alkenyl-2-hydroxy-1,4-quinones are the main precursors for the preparation of dihydrofuro- and furonaphthoquinones.[2]

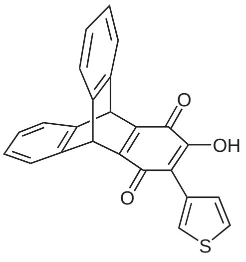
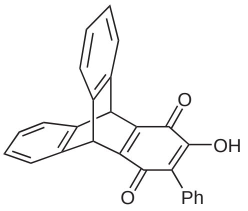
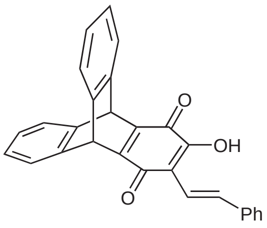
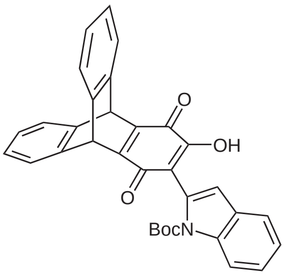
In all the cases outlined in Table 2, compounds of type PhAr were by-products of the reaction in yields varying from 45–90%. As mentioned in the case of **6a**, these products arise from the coupling reaction of iodobenzene, produced in the main reaction, with an excess of $ArB(OH)_2$, as it was proved by a control reaction.[10]

The coupling reaction did not proceed at all with phenyliodonium ylides of some other 2-hydroxyquinones, such as 5-methyl- and 5,6-dimethyl-2-hydroxy-1,4-benzoquinone.[3b] In contrast, the corresponding ylide of hydroxytriptycenequinone[3e] **9** afforded the coupling products **10** (Table 3).

In this case yields are rather low but the reaction allows access to functionalized triptycenequinones, a class of compounds with interesting biological activity.[11]

Table 3 Coupling Reaction of Phenyliodonium Ylide of Hydroxytriptycenequinone (**9**) with $ArB(OH)_2$



$ArB(OH)_2$	Coupling product	Yield (%)
6a	 **10a**	22
6b	 **10b**	13
6e	 **10e**	33
6g	 **10g**	34

In summary, the transformation of 2-hydroxyquinones to their 3-substituted derivatives can be most conveniently achieved in two steps: formation of their phenyliodonium ylides[3] and Suzuki-type coupling reaction of the latter with aryl- and alkenylboronic acids. The high yields, the diversity of both reaction steps, and the possibility of conducting the second step in water could make this the method of choice for the preparation of this interesting class of compounds.

References and Notes

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(6) Zhu, Q.; Wu, J.; Fathi, R.; Yang, Z. *Org. Lett.* **2002**, *4*, 3333.

(7) (a) Transylidation reactions of zwitterionic iodonium compounds are well known, see: Varvoglis, A. In *The Organic Chemistry of Polycoordinated Iodine*; VCH: New York, **1992**. (b) In our case the side-reaction with phosphines is described in Scheme 2.

(8) **Coupling Reaction of Ylides 5 and 9 with Arylboronic Acids 6; General Procedure.** A degassed solution of arylboronic acid (1.1 mmol) and P(*t*-Bu)$_3$ (0.1 mmol) in DME–H_2O (4:1, 10 mL) was added to a degassed flask containing a mixture of ylide **5** or **9** (0.5 mmol), LiOH·H_2O (2.7 mmol), and Pd(OAc)$_2$ (6 mg, 4 mmol%) and the resulting suspension was stirred at r.t. under Ar for 5 h. The solution was acidified to pH 6 by the addition of 4–5 drops of acetic acid and excess DME was evaporated. CH_2Cl_2 (10 mL) was added and the suspension was filtered through filter paper, which was moistened with CH_2Cl_2 (1–2 mL). The filtrate was dried, concentrated, and subjected to column chromatography (silica gel, hexanes–EtOAc, 3:1) to afford the coupling products **7** and **10**. **2-Hydroxy-3-(3-thienyl)-1,4-naphthoquinone (7a)**: Mp 126–127 °C. IR (KBr): 3322, 1650, 1590 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.16 (1 H, d, *J* = 8.0 Hz), 8.10 (1 H, br s), 8.08 (1 H, d, *J* = 8.0 Hz), 7.94 (1 H, s), 7.80–7.65 (3 H, m), 7.35 (1 H, d, *J* = 4.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 183.8, 181.6, 151.5, 135.2, 133.1, 130.0, 129.7, 129.5, 129.1, 127.3, 126.0, 124.0, 123.2, 116.9. MS (EI): *m*/*z* (%) = 256 (100) [M$^+$], 228 (68), 184 (25), 171 (71). Anal. Calcd for $C_{14}H_8O_3S$: C, 65.61; H, 3.15. Found: C, 65.37; H, 3.19.

(9) For a recent review on Suzuki coupling reactions in water, see: Leadbeater, N. E. *Chem. Commun.* **2005**, 2881.

(10) The coupling reaction was repeated exactly under the previously described conditions, using 1 mmol of iodobenzene instead of ylide **5**

(11) (a) Perchellet, E. M.; Magill, M. J.; Huang, X.; Brantis, C. E.; Hua, D. H.; Perchellet, J.-P. *Anti-Cancer Drugs* **1999**, *10*, 749. (b) Xanthopoulou, N. J.; Kourounakis, A. P.; Spyroudis, S.; Kourounakis, P. N. *Eur. J. Med. Chem.* **2003**, *38*, 621. (c) Xua, D. H.; Tamura, M.; Huang, X.; Stephany, H. A.; Helfrich, B. A.; Perchellet, E. M.; Sperfslage, B. J.; Perchellet, J.-P.; Jiang, S.; Kyle, D. E.; Chiang, P. K. *J. Org. Chem.* **2002**, *67*, 2907.