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"On Water"-Promoted Direct Coupling of Indoles with 1,4-Benzoquinones without Catalyst

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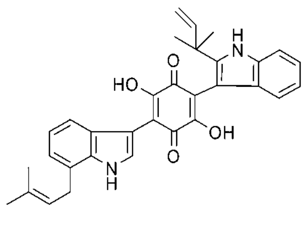
A highly efficient direct coupling of indole compounds with 1,4-benzoquinones was developed "on water" in the absence of any catalyst, organic co-solvent, or additives. The "on-water" conditions provided the best yields of the corresponding products and the only system to produce bis(coupling) products.

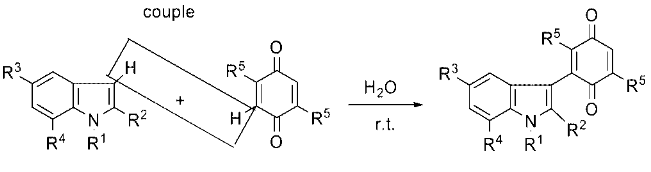
Recently, organic reactions performed in water have attracted considerable attention[1] not only in light of growing environmental concerns, but also with respect to the unique properties of water in promoting reactions and enhancing selectivities. In his pioneering work on aqueous Diels–Alder reaction, Breslow[2] showed in 1980 that the reaction of cyclopentadiene with butenone in water was more than 700 times faster than the same reaction in isooctane. In 2004, Pirrung[3] reported that multicomponent reactions, such as the Passerini and Ugi reactions were accelerated in water. These water-accelerating effects have been attributed to the hydrophobic effect in the aqueous phase. More recently, Sharpless[4] reported that several cycloaddition reactions and non-pericyclic reactions can proceed in pure water with substantial rate acceleration even though water-insoluble substrate was used in a suspension (denoted as "on water" conditions).

On the other hand, 3-indolylquinone, especially bis(indolyl)quinone, is an important structural unit in many natural products with biological and pharmaceutical activities.[5] Among them, the asterriquinones found in fungi exhibit a number of biological activities, including antitumor properties[6] and inhibition of HIV reverse transcriptase.[7] Recently, demethylasterriquinone B1 was found to be a non-protein, orally active insulin mimetic[8]. It is also interesting to note that asterriquinone molecules consist of two prenylated indoles appended to a dihydroxyquinone core. Therefore, the synthesis of bis(3-indolyl)quinones has attracted considerable attention. The direct coupling of indole compounds with 1,4-benzoquinones, which can be catalyzed by protic acids (HCl, H_2SO_4 and CH_3CO_2H)[9] and Lewis acids [such as $InBr_3$[10] and $Bi(OTf)_3$[11]] in an organic solvent, provided the most direct approach to 3′-indolylquinones. However, the synthesis of bis(indolyl)-1,4-benzoquinone has been rarely reported. More recently, Pirrung reported the synthesis of bis(indolyl)-1,4-benzoquinone under relatively intense reaction conditions: using $Zn(OTf)_2$ (1 equiv.) as catalyst and THF as solvent, refluxing for 26 h under nitrogen followed by oxidation with DDQ,[12] or by coupling with mercury reagents catalyzed by Pd^{II}/$Cu(OAc)_2$.[13]



Demethylasterriquinone B1

We report herein a highly efficient "on water"-promoted direct coupling of indole compounds with 1,4-benzoquinones (Scheme 1) without the use of any catalyst, additive, or organic solvent. A notable water acceleration was observed in these reactions, even though the reactants were in a heterogeneous reaction system, which provided an efficient method for the synthesis of bis(indolyl)-1,4-quinones.



Scheme 1. "On water"-promoted direct coupling of indoles with quinones.

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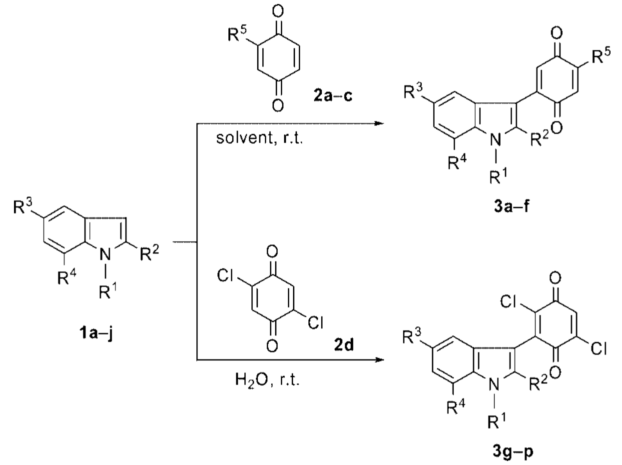
Initially, the reaction of 2-methylindole (**1a**: R^1, R^3, R^4 = H, $R^2 = CH_3$) with 1,4-benzoquinone (**2a**; **1a**/**2a** = 1:2) was carried out in various solvents at room temp. for 10 h without using any catalyst (Scheme 2 and Table 1). In organic solvents, such as dichloromethane, acetonitrile, THF, ethanol, and toluene, the yields of the coupled product, 2-(2′-methylindol-3-yl)-1,4-benzoquinone (**3a**: R^1, R^3, R^4, R^5 = H, $R^2 = CH_3$) were very poor (Entries 1–6), even though the reaction system was completely homogeneous. When aqueous THF and ethanol were used as the reaction media, the yields of **3a** increased (Entries 7–8). Under solvent-free conditions, the yield of **3a** was also low (Entry 11). It is interesting to note that when water alone was used as solvent under the same conditions, the yield of **3a** reached 82% (Entry 9), which is better than when any organic solvent was used (either polar, nonpolar, or aqueous organic solvent). *The reactants were insoluble in water, forming an aqueous suspension by vigorous stirring*. No molten starting materials were observed during the reaction when both reactants are solid. To explain the experimental results in the reaction on water, it is possible that one of the slightly soluble reagents reacts with the insoluble reagent on the surface of its solid. The equilibrium was shifted to the product continuously even when the product was also insoluble in water. Increasing the reaction temperature to 50 °C decreased the yield (Entry 10). The use of an aqueous LiCl (2.5 M) or a solution of glucose (1 M *in* water) as reaction media neither changed the yield of **3a** in an aqueous reaction nor accelerated the reaction.[14]



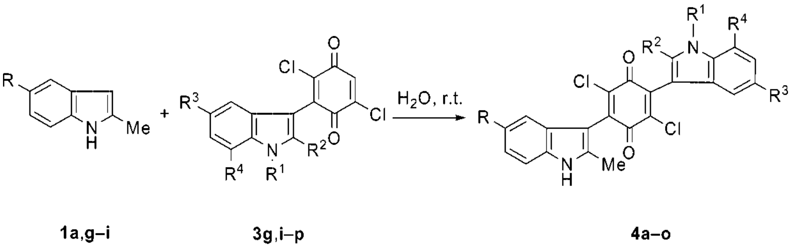
Scheme 2.

Table 1. Reaction of **1a** with **2a** in various solvents.[a]

Entry	Solvent	Yield of **3a** (%)[b]
1	CH_2Cl_2	13
2	CH_3CN	–[c]
3	Et_2O	–[c]
4	THF	–[c]
5	toluene	trace
6	C_2H_5OH	38
7	THF/H_2O (1:2)[d]	55
8	C_2H_5OH/H_2O (10:1)[d]	51
9	H_2O[d]	82
10	H_2O[e]	39
11	–[f]	20

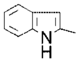
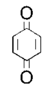
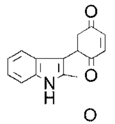
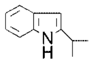
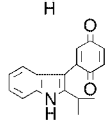
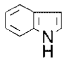
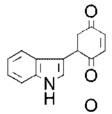
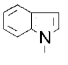
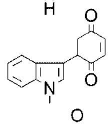
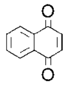
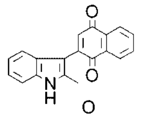
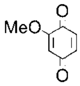
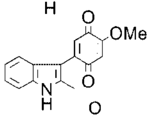
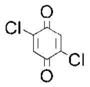
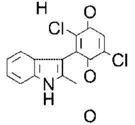
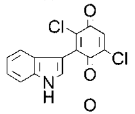
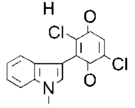
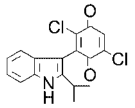
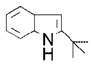
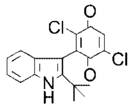
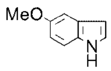
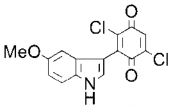
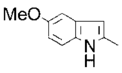
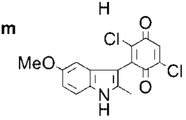
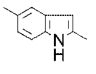
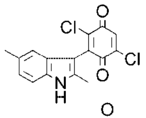
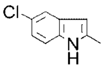
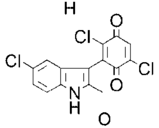
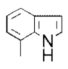
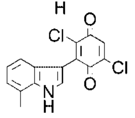
[a] Room temperature for 10 h. [b] Isolated yield. [c] No product was detected. [d] Aqueous suspension. [e] At 50 °C. [f] Solvent-free conditions.

Based on these results, various indole derivatives (**1a**–**j**) reacted with 1,4-benzoquinones (**2a**–**d**) in neutral water (deionized and redistilled three times) at room temperature without using any catalysts or additives (Scheme 2). The reaction proceeded smoothly to give the coupling products (**3a**–**p**) in good yields (58–84%) (Table 2). *The scale-up experiment of the reaction of **1j** with **2d** was performed on a 600 mg scale to give the product **3p** in quantitative yield. The blue product floated on the colorless water phase, when the reaction was complete and the stirring stopped.* The nature of the substituents on the indole ring strongly influences the reactivity of indole substrates. The presence of a bulky group at the 2-position of the indole ring reduced the reactivity [compare methyl (**1a**), isopropyl (**1b**) and *tert*-butyl (**1e**) substituents]. Having an electron-withdrawing group at the 5-position of the indole ring also reduced the reactivity, prolonged the reaction time to 16 h and generated a lower yield of the coupled product (Entry 15). Interestingly, in the reactions of **2d** with **1a**, **1g** or **1h**, bis(indolyl)quinones products **4a**, **4b** and **4c** were obtained in 48–53% yields (Entries 7, 13 and 14), whereas the same reaction in an organic solvent did not give bis(indolyl)quinone products at all. In comparison, the reactions of **1a** with **2d** were carried out in dichloromethane and THF under the same conditions at room temp. for 12 h without any catalyst. In CH_2Cl_2, only trace amounts of the monosubstituted product and no disubstituted product were detected. In THF, neither the mono- nor the disubstituted product was observed, and the starting materials were recovered. Moreover, if the ratio of **1a**/**2a** was changed from 1:2 to 1:1, the coupling reaction (room temp., 28 h) provided bis(indolyl)-1,4-benzoquinone



Scheme 3.

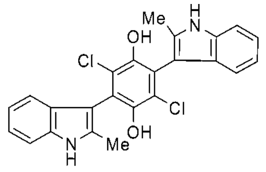
Table 2. Reaction of indoles (**1a–j**) with quinones (**2a–d**) in water without catalyst.

Entry	Indole[a]		Quinone[a]		Time (h)	Product		Yield[b] (%)
1	**1a**		**2a**		10	**3a**		82
2	**1b**		**2a**		12	**3b**		78
3	**1c**		**2a**		24	**3c**		58
4	**1d**		**2a**		24	**3d**		67
5	**1a**		**2b**		14	**3e**		84
6	**1a**		**2c**		24	**3f**		72
7	**1a**		**2d**		12	**3g**	 + **4a**[c]	31+49
8	**1c**		**2d**		28	**3h**		67
9	**1d**		**2d**		28	**3i**		70
10	**1b**		**2d**		12	**3j**		78
11	**1e**		**2d**		48	**3k**		60
12	**1f**		**2d**		16	**3l**		65
13	**1g**		**2d**		12	**3m**	 + **4b**[c]	30+53
14	**1h**		**2d**			**3n**	 + **4c**[c]	34+48
15	**1i**		**2d**		16	**3o**		58
16	**1j**		**2d**		24	**3p**		75

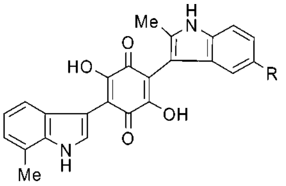
[a] Indole/quinone = 1:2. [b] Isolated yield. [c] Bis(indolyl)quinone products, see Table 3.

4a (53%) and bis(indolyl)-1,4-hydrobenzoquinone **5a** (27%). Prolonging the reaction time to 48 h increased the yield of **4a** to 73%, whereas the reaction of **1h** with **2d** (**1h**/**2d** = 1:1) gave the homo-bis(indolyl)-1,4-quinone compound **4c** in 70% yield. The results indicate that the mono-indolylquinone intermediate formed during the course of the reaction exhibits a higher reactivity with another molecule of indole substrate in water than in an organic solvent and double coupling of indoles with 2,5-dichloro-1,4-benzoquinone (**2d**) can be realized under "on water" conditions. Based on these observations, the synthesis of various homo- and cross-bis(indolyl)quinones was investigated.

At first, the reactions of **1a** with **3p** (**1a**/**3p** = 1:2) were carried out in various solvents without using any catalyst (Scheme 3). The results listed in Table 3 show that using water as the reaction medium also provided the highest yield (86%) of bis(indolyl)quinone product **4e**. Homo-bis(indolyl)quinones **4a–d** and cross-bis(indolyl)quinones **4e–o** were synthesized in 68–90% and 72–92% yields (Table 4), respectively, at room temperature for 24–30 h without using a catalyst. The products, 2,5-dichloro-bis-(indolyl)quinones **4f–g**, were then converted into 2,5-dihydroxybis(indolyl)quinones **6a–b** in 62–70% yields by hy-



5a



6a: R = CH_3, 70%
6b: R = OCH_3, 62%

Table 3. Reaction of **1a** with **3p** in various solvents.[a]

Entry	Solvent	Yield of **4e** (%)[b]
1	CH_2Cl_2	–[c]
2	THF	–[c]
3	C_2H_5OH	36
4	C_2H_5OH/H_2O (1:1)	50
5	C_2H_5OH/H_2O (1:10)[d]	73
6	H_2O[d]	86

[a] At room temp. for 24 h. [b] Isolated yield. [c] No product was detected. [d] Aqueous suspension.

Table 4. Synthesis of bis(indolyl)-1,4-quinones (**4a–o**) in water.

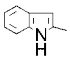
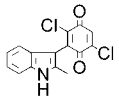
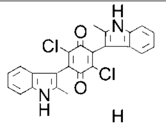
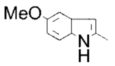
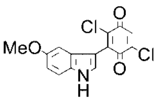
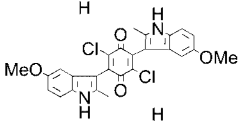
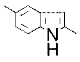
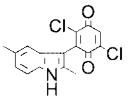
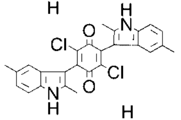
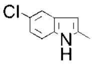
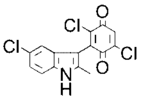
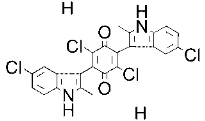
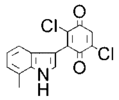
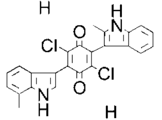
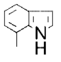
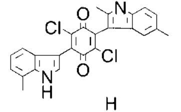
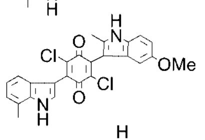
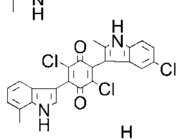
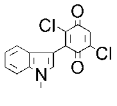
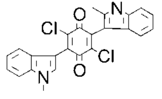
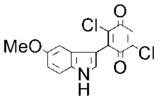
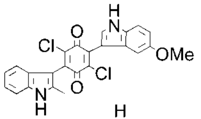
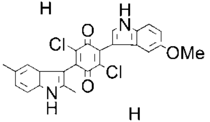
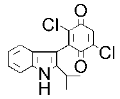
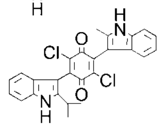
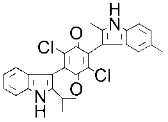
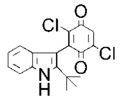
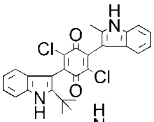
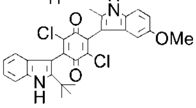
Entry	Indole[a]	Quinone[a]	Time (h)	Product	Yield[b] (%)
1	**1a** 	**3g** 	24	**4a** 	90
2	**1g** 	**3j** 	24	**4b** 	83
3	**1h** 	**3n** 	24	**4c** 	68
4	**1i** 	**3o** 	30	**4d** 	68
5	**1a**	**3p** 	24	**4e** 	86
6	**1h** 	**3p**	24	**4f** 	87
7	**1g**	**3p**	24	**4g** 	85
8	**1i**	**3p**	24	**4h** 	77
9	**1a**	**3i** 	24	**4i** 	86

Table 4. *(Continued)*

Entry	Indole[a]	Quinone[a]	Time (h)	Product	Yield[b] (%)
10	**1a**	**3l** 	24	**4j** 	76
11	**1h**	**3l**	24	**4k** 	85
12	**1a**	**3j** 	24	**4l** 	92
13	**1h**	**3j**		**4m** 	90
14	**1a**	**3k** 	30	**4n** 	72
15	**1g**	**3k**	30	**4o** 	80

[a] Indole/quinone = 1:2. [b] Isolated yield.

drolyzing the substrates in refluxing 10% NaOH/MeOH for 0.5 h.[12]

In conclusion, a highly efficient direct coupling of indole compounds with 1,4-benzoquinones was developed "on water" without using any catalyst, organic co-solvent, or additives. The "on water" conditions provided the best yields of the corresponding products. Without using a catalyst, "on water" is the only system that can provide the desired bis(coupling) product. The scope and synthetic application of the method is under investigation.

Acknowledgments

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