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$Bi(OTf)_3$-catalyzed conjugate addition of indoles to *p*-quinones: a facile synthesis of 3-indolyl quinones

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Abstract—A wide range of indoles undergo conjugate addition to *p*-benzoquinones in the presence of 2 mol% bismuth triflate under mild conditions to afford the corresponding 3-indolyl quinones in excellent yields with high selectivity.

The 3-indolylbenzoquinone fragment is a core structure in a number of biologically active natural products such as asterriquinones.[1] The asterriquinones and demethylasterriquinones exhibit a wide spectrum of biological activities including antitumor properties and are inhibitors of HIV reverse transcriptase.[2] Asterriquinone A1, has been shown to arrest the cell cycle in G_1 and promote apoptotic cell death.[3] Recently, asterriquinone has been reported as an orally active non-peptidyl mimetic of insulin with antidiabetic activity.[4] All these properties apparently stem from the ability of asterriquinones to either promote or prevent protein–protein interactions. Bisindolyl quinones (Fig. 1) have been isolated from a wide range of fungi, including *Aspergillus terreus*, *Chaetomium* sp., and *Pseudomassaria* sp.[5]

The simplest and the most straightforward approach for the synthesis of indol-3-ylbenzoquinones involves the condensation of indoles with quinones under acidic conditions.[6,7]

Recently, bismuth(III) triflate has attracted the attention of synthetic organic chemists because it is inexpensive and it can be easily prepared even on multi-gram scale in the laboratory from commercially available bismuth(III) oxide and triflic acid.[8] Owing to its unique catalytic properties, bismuth(III) triflate has been extensively used for a plethora of organic transformations.[9] However, there have been no reports on the conjugate addition of indoles to *p*-quinones employing bismuth triflate as a catalyst.

In this report, we wish to describe a simple, convenient and efficient protocol for the synthesis of indol-3-ylbenzoquinones using a catalytic amount of $Bi(OTf)_3$ under mild conditions. For example, treatment of indole **1** with 2,5-dichloro-*p*-benzoquinone **2** in the presence of 2 mol% of $Bi(OTf)_3$ led to the formation of 3-indolyl-2,5-dichlorohydroquinone **3a** in 85% yield (Scheme 1).

Similarly, treatment of 2,5-dichloro-*p*-benzoquinone or *p*-benzoquinone with 5-methoxy-, 5-bromo-, 7-ethyl-, 2-methyl- and ethyl 2-carboxyindoles afforded the corresponding indol-3-yl hydroquinones (entries **3b–g**,

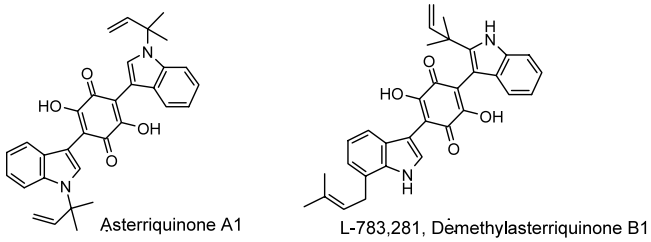
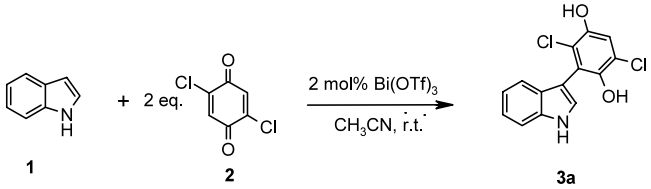


Figure 1.



Scheme 1.

Keywords: *p*-quinones; indoles; bismuth triflate; indol-3-ylbenzoquinones.

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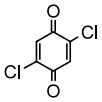
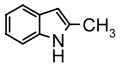
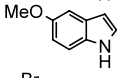
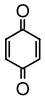
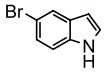
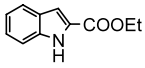
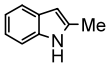
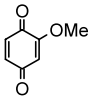
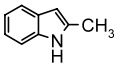
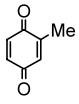
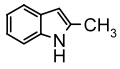
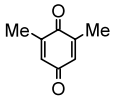
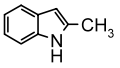
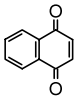
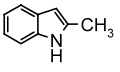
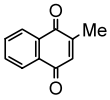
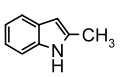
Table 1). Interestingly, the reaction of indole with *p*-benzoquinone gave 2,5-bis(3-indolyl)-1,4-hydroquinone **4h** in 82% yield under similar reaction conditions (Scheme 2).

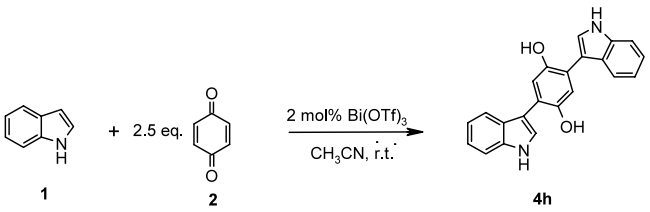
However, substituted quinones such as 2-methyl-, 2-methoxy-, and 2,6-dimethyl-*p*-benzoquinones reacted smoothly with indole and 2-methylindole to give the corresponding indol-3-ylbenzoquinones in high yields (entries **5i**–**n**, Table 1, Scheme 3).

In the case of mono-substituted quinones, the indole regioselectively added to the quinones at the less hindered position which was confirmed by ^{1}H NMR spec-

Table 1. Bismuth(III) triflate catalyzed addition of indoles to *p*-quinones

Entry	Indole	Quinone	Product[a]	Time (min)	Yield(%)[b]
a			**3a**	30	85
b		"	**3b**	25	87
c			**3c**	15	93
d		"	**3d**	25	75
e		"	**3e**	35	78
f		"	**3f**	20	90
g		"	**3g**	12	91
h		"	**4h**	20	82[c]
i			**5i**	20	80[d]
j		"	**5j**	15	85[d]
k			**5k**	25	82[d]
l		"	**5l**	15	88[d]
m			**5m**	40	80
n		"	**5n**	25	84
o			**6o**	45	82
p		"	**6p**	30	87
q			**6q**	40	78
r		"	**6r**	35	85

a: All products were characterized by ^{1}H NMR, IR and mass spectroscopy.
b: Isolated and unoptimized yields.
c: *bis*-Indolylquinone was isolated.
d: Indole was added to quinone at less hindered position.



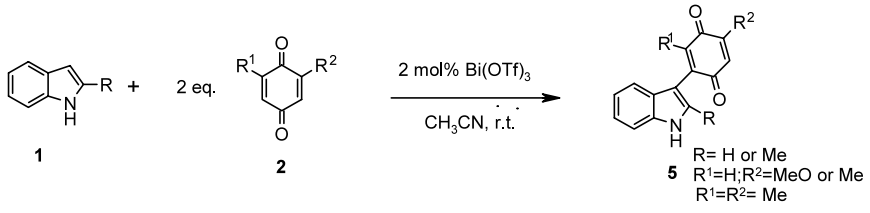
Scheme 2.

trum of the products (entries **5i**, **5j**, **5k**, **5l**, Table 1). Like the substituted quinones (Scheme 3), 1,4-naphthoquinone and 2-methyl-1,4-naphthoquinone afforded 2-(3-indolyl)-1,4-naphthoquinone derivatives under identical conditions (entries **6o**–**r**, Table 1, Scheme 4)[10].

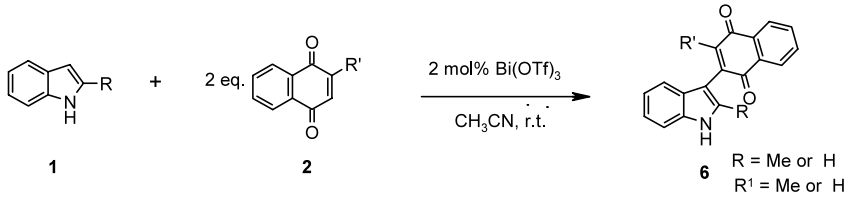
In all cases, the reactions proceeded rapidly at room temperature with high regioselectivity. As solvent, acetonitrile appeared to give the best results. The products were characterized by ^{1}H, ^{13}C NMR, IR and mass spectroscopic data and also by comparison with authentic samples.[7b] The probable mechanism seems to be the addition of the indole to the unsaturated position of the quinone, which is activated by bismuth triflate. The initial addition product tautomerizes to the hydroquinone which subsequently undergoes rapid oxidation with another equivalent of *p*-quinone resulting in the formation of the indol-3-ylquinone (Scheme 5).

This method is clean and free from the chlorinated side products which are normally observed under protic acid (conc. HCl in THF) conditions. This method also works well with the electron-deficient ethyl 2-carboxyindole to give the corresponding indol-3-ylhydroquinone **3e** in fairly good yield. However, most other methods fail to produce 3-indolylquinones with electron-deficient indoles. Thus, this method is an efficient and very useful synthetic procedure for the synthesis of natural product core structures. Among the various metal triflates such as $Cu(OTf)_2$, $Yb(OTf)_3$, $In(OTf)_3$ and $Ce(OTf)_3$ studied for this transformation, bismuth(III) triflate was found to be the most effective in terms of conversion and reaction rates. However, similar yields and selectivity were also obtained using 5 mol% of scandium(III) triflate under these reaction conditions. The scope and generality of this process is illustrated with respect to various indoles and a wide range of quinones and the results are presented in Table 1.[11]

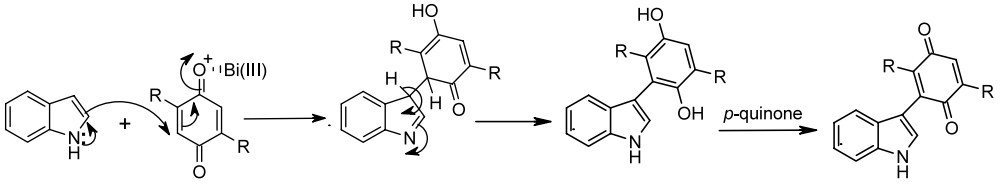
In summary, we describe a simple and highly efficient protocol for the preparation of 3-indolylquinones through the nucleophilic addition of indoles to quinones using bismuth(III) triflate as a catalyst. This method is applicable to both electron-rich as well as electron-deficient indoles and can be applied to the total synthesis of naturally occurring asterriquinones.



Scheme 3.



Scheme 4.



Scheme 5.

Acknowledgements

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11. ***General procedure***: A mixture of the *p*-quinone (2.5 mmol) and $Bi(OTf)_3$ (2 mol%) or $Sc(OTf)_3$ (5 mol%) and indole (1 mmol) in acetonitrile (10 mL) was stirred at room temperature for the specified time (see Table 1). After completion of the reaction as indicated by TLC, the reaction mixture was quenched with water (15 mL) and extracted with dichloromethane (2×10 mL). Evaporation of the solvent followed by purification on silica gel (Merck, 100–200 mesh, ethyl acetate-hexane, 0.5–9.5) afforded pure indol-3ylbenzoquinone. Spectral data for selected products: **3g**: 2-(2-methyl-3-indolyl)-1,4-hydroquinone (see Table 1): solid, mp 106–108°C, ^{1}H NMR ($CDCl_3$): δ 2.40 (s, 3H), 4.40 (brs, 1H, OH), 4.60 (brs, 1H, OH), 6.70–6.80 (m, 2H), 6.90 (d, 1H, $J=8.0$ Hz), 7.05–7.20 (m, 2H), 7.30–7.45 (m, 2H), 8.0 (brs, 1H, NH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 12.9, 109.9, 110.8, 114.3, 116.1, 116.8, 118.3, 118.9, 120.5, 122.9, 128.3, 133.3, 135.6, 147.8, 149.8. IR (KBr): ν 3279, 2923, 1636, 1565, 1457, 1294, 1010, 774 cm^{-1}. EIMS: m/z (%): 239 M^+ (30), 155 (10), 141 (20), 199 (100), 82 (95), 47 (80). HRMS calcd for $C_{15}H_{13}NO_2$: 239.0946. Found: 239.0989. **4h**: 2,5-bis(3-indolyl)-1,4-hydroquinone (see Table 1): solid, mp 116–118°C, ^{1}H NMR ($CDCl_3$): δ 4.80 (brs, 2H, OH), 7.05 (d, 2H, $J=1.7$ Hz), 7.05–7.45 (m, 8H), 7.80 (d, 2H, $J=8.1$ Hz), 8.30 (brs, 2H, NH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 112.8, 113.9, 116.9, 117.6, 120.2, 122.2, 124.2, 126.5, 127.2, 137.3, 147.9. IR (KBr): ν 3398, 1618, 1457, 1337, 1096, 743 cm^{-1}. EIMS: m/z (%): 340 M^+ (100), 257 (10), 228 (12), 156 (15), 142 (70), 84 (80), 47 (20). HRMS calcd for $C_{22}H_{16}N_2O_2$: 340.3689. Found: 340.3095. **5l**: 2-methyl-5-(2-methyl-3-indolyl)benzo-1,4-quinone (see Table 1): solid, mp 196–197°C, ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.15 (s, 3H), 2.40 (s, 3H), 6.70 (s, 1H), 6.85 (s, 1H), 7.05–7.20 (m, 2H), 7.25–7.30 (m, 1H), 7.45–7.50 (m, 1H), 8.10 (brs, 1H, NH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.6, 15.4, 105.9, 111.2, 119.2, 120.1, 121.5, 127.6, 132.9, 133.8, 138.3, 142.3, 145.4, 146.3, 187.2, 187.8. IR (KBr): ν 3398, 1616, 1457, 1219, 772 cm^{-1}. EIMS: m/z (%): 251 M^+ (40), 186 (50), 154 (30), 121 (40), 77 (100), 41 (40). **6p**: 2-(2-methyl-3-indolyl)-1,4-naphthoquinone (see Table 1): solid, mp 180°C, ^{1}H NMR ($CDCl_3$): δ 2.50 (s, 3H), 7.10 (s, 1H), 7.15–7.20 (m, 2H), 7.25–7.30 (m, 1H), 7.50–7.60 (m, 1H), 7.70–7.80 (m, 2H), 8.10–8.20 (m, 2H), 8.25 (brs, 1H, NH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.2, 107.6, 111.1, 119.7, 121.2, 122.6, 126.3, 127.4, 128.0, 132.6, 133.2, 133.9, 134.1, 135.1, 135.9, 137.5, 144.8, 185.2, 185.7. IR (KBr): ν 3274, 2922, 1739, 1634, 1457, 1254, 714 cm^{-1}. EIMS: m/z (%): 287 M^+ (20), 270 (15), 230 (100). HRMS calcd for $C_{19}H_{13}NO_2$: 287.0946. Found: 287.0918.