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Synthesis of hydroxybenzofurans by condensation of quinones with benzoylacetone: revised structure of the adducts

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ABSTRACT

The copper(II) triflate-catalyzed condensation of diketones with quinones has been reported to efficiently yield 3-acyl-5-hydroxybenzofurans. We found that the reported structure of the adducts resulting from the condensation of benzoylacetone should be revised to be the 2-methyl-3-benzoyl isomers.

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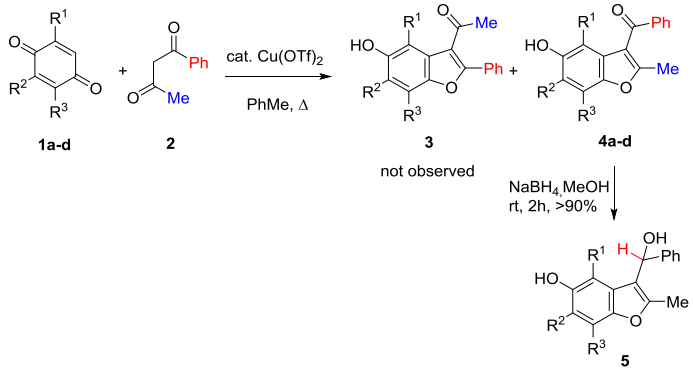
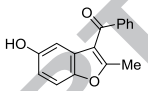
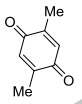
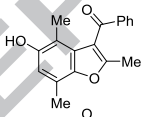
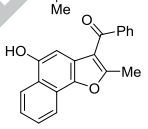
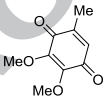
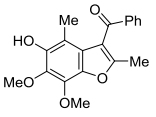
Benzofurans are featured as structural motifs within various natural products and are also of prime interest as drug candidates in biological and pharmaceutical research.[1-11] During our medicinal chemistry program aiming at developing novel anticancer hydroxybenzofurans,[10,11] we used a remarkably convenient method that relies on copper(II) triflate-catalyzed cascade formal [3 + 2] cycloaddition of 1,4-benzoquinones with 1,3-dicarbonyl compounds (Scheme 1).[12] In the course of this study, we got intrigued by the reported regioselectivity observed with the benzoylacetone and we reexamined this reaction. For the ease of purification, we collected only adduct **4** that precipitated



Scheme 1. $Cu(OTf)_2$-catalyzed condensation of quinones with benzoylacetone.

in the reaction mixture.[13] The expected isomer **3** was not detected by NMR analysis of the mother liquors.[14] Ketones **4** were reduced to alcohols **5** using $NaBH_4$, and the formed methine hydrogen (red) appeared as a singlet in their ^1H NMR spectrum, and not as a quadruplet, which unambiguously confirmed the structure of these compounds.[15] The structure of **4a** was further confirmed by Noesy experiment.

Table 1. Formation of hydroxybenzofurans **4** from quinones **1** (Scheme 1).

Entry	1	4	Yield % [a]
a			46
b			49
c			26
d			42

[a] based on the precipitation in Et_2O.

In conclusion, the formal [3 + 2] cycloaddition of 1,4-benzoquinones with benzoylacetone yield to 2-methyl-3-benzoyl-5-hydroxybenzofurans **4**, and not to their 3-acyl-2-phenyl isomers **3** as originally reported. Interestingly, the same regioisomers were observed in the Nenitzescu condensation of *p*-benzoquinone with β-(dimethylamino)vinylketones or in the $ZnCl_2$-catalyzed condensation of naphtoquinone with benzoylacetone.[16,17]

Acknowledgments

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Supplementary Material

Supplementary data (NOESY experiment of compound **4a**) associated with this article can be found, in the online version, at http://

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13. Typical experimental procedure for the synthesis of **4**: To a suspension of **2** (14.69 mmol) and $Cu(OTf)_2$ (5 mol %) in toluene (10 mL) under an argon atmosphere was added slowly a solution of **1** (7.34 mmol) in toluene (10 mL). The reaction mixture was stirred at reflux for one night (~15 hours), quenched with 50 mL of saturated NH_4Cl solution and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Diethyl ether (20 mL) was added and the precipitate was collected by filtration to give the title compound **4**. Compound **4a**: brown solid; ^1H NMR ($CDCl_3$, 400 MHz): 7.78 (d, 2H, *J* = 7.6 Hz), 7.60 (t, 1H, *J* = 7.2 Hz), 7.49 (t, 2H, *J* = 7.6 Hz), 7.30 (d, 1H, *J* = 8.8 Hz), 7.06 (d, 1H, *J* = 2.4 Hz), 6.81 (dd, 1H, *J* = 2.4 Hz, 8.8 Hz), 5.51 (s, 1H), 2.44 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): 192.4, 163.1, 152.5, 148.6, 139.3, 132.6, 128.9, 128.6, 127.8, 117.0, 113.0, 111.3, 106.6, 15.0. Compound **4b**: brown solid; ^1H NMR ($CDCl_3$, 400 MHz):

7.87 (d, 2H, *J* = 8.0 Hz), 7.58 (t, 1H, *J* = 7.6 Hz), 7.45 (t, 2H, *J* = 7.6 Hz), 6.62 (s, 1H), 4.59 (s, 1H), 2.44 (s, 3H), 2.35 (s, 3H), 1.91 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): 193.2, 158.0, 149.7, 147.7, 139.1, 133.3, 129.6, 128.7, 126.9, 118.9, 118.1, 113.9, 112.4, 14.7, 13.9, 12.7. Compound **4c**: white solid; ^{1}H NMR (DMSO, 400 MHz): 9.99 (s, 1H), 8.13 (d, 1H, *J* = 8.4 Hz), 8.08 (d, 1H, *J* = 8.4 Hz), 7.73 (d, 2H, *J* = 7.4 Hz), 7.65-7.42 (m, 5H), 6.87 (s, 1H), 2.43 (s, 3H). ^{13}C NMR (DMSO, 100 MHz): 191.8, 161.0, 150.6, 142.7, 139.4, 133.2, 129.3, 129.2, 127.7, 124.9, 123.7, 123.2, 122.9, 120.9, 119.5, 117.9, 100.2, 15.2. Compound **4d**: orange oil; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.68 (d, 2H, *J* = 7.6 Hz), 7.38 (t, 1H, *J* = 7.6 Hz), 7.26 (t, 2H, *J* = 7.6 Hz), 5.61 (s, 1H), 3.95 (s, 3H), 3.78 (s, 3H), 2.15 (s, 3H), 1.71 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): 192.9, 157.1, 144.1, 139.6, 138.8, 136.3, 133.4, 131.2, 129.6, 128.7, 123.5, 118.0, 108.9, 61.6, 60.9, 13.8, 12.6.

14. NMR analysis of the mother liquors indicated the presence of a substantial amount of quinones hydroxybenzofurans **4**, but not of their isomers **3.**
15. Typical procedure for the synthesis of **5**: $NaBH_4$ (0.92 mmol) was added to a solution of **4** (0.46 mmol) in anhydrous MeOH (5 mL) and the mixture was stirred at r.t. for 2 hours. The reaction was concentrated under reduced pressure, washed with aq. solution of HCl 1N (10 mL) and extracted with DCM (2x 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by flash silica gel column chromatography (DCM/ether as eluent) to give alcohol **5**. **5a**: white solid; ^{1}H NMR (DMSO, 400 MHz): 8.93 (s, 1H), 7.43 (d, 2H, *J* = 7.6 Hz), 7.31 (t, 2H, *J* = 7.6 Hz), 7.22-7.17 (m, 2H), 6.76 (d, 1H, *J* = 2.4 Hz), 6.57 (dd, 1H, *J* = 2.4 Hz, *J* = 7.6 Hz), 5.88 (d, 1H, *J* = 3.5 Hz), 5.78 (d, 1H, *J* = 3.5 Hz), 2.46 (s, 3H). ^{13}C NMR (DMSO, 100 MHz): 153.0, 151.7, 147.9, 144.8, 128.6, 128.4, 127.1, 126.2, 118.5, 111.9, 110.8, 105.9, 67.3, 12.8. **5b**: white solid; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.27-7.13 (m, 6H), 6.45 (s, 1H), 6.14 (s, 1H), 4.37 (s, 1H), 2.31 (s, 3H), 2.28 (s, 3H), 1.96 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): 153.8, 149.1, 148.2, 142.8, 128.3, 127.1, 126.6, 126.1, 118.6, 117.2, 113.2, 112.2, 68.0, 14.7, 13.0, 12.5. **5c**: yellow solid; ^{1}H NMR (DMSO, 400 MHz): 9.72 (s, 1H), 8.13 (d, 1H, *J* = 8.4 Hz), 8.05 (d, 1H, *J* = 8.4 Hz), 7.55 (t, 1H, *J* = 7.5 Hz), 7.47 (d, 2H, *J* = 7.5 Hz), 7.41 (t, 1H, *J* = 7.5 Hz), 7.33 (t, 2H, *J* = 7.5 Hz), 7.22 (t, 1H, *J* = 7.5 Hz), 6.97 (s, 1H), 5.98 (s, 1H), 5.91 (s, 1H), 2.57 (s, 3H). ^{13}C NMR (DMSO, 100 MHz): 150.4, 148.9, 144.9, 142.8, 128.5, 127.1, 127.0, 126.3, 123.9, 123.6, 123.5, 122.6, 121.1, 119.9, 119.3, 101.0, 67.4, 12.9. **5d**: orange solid; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.27-7.15 (m, 5H), 6.12 (s, 1H), 5.59 (s, 1H), 4.01 (s, 3H), 3.84 (s, 3H), 2.34 (brs, 1H), 2.24 (s, 3H), 1.99 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): 153.3, 143.3, 142.7, 140.1, 135.8, 134.8, 128.3, 127.2, 126.1, 123.4, 117.2, 108.9, 67.9, 61.5, 60.9, 13.1, 12.4.
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Graphical Abstract

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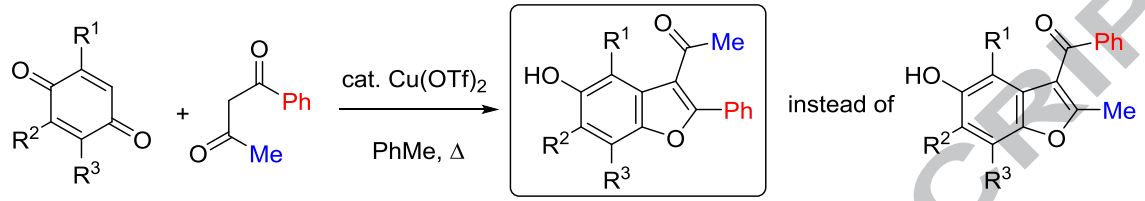

Highlights

- The condensation of diketones with quinones is known to yield hydroxybenzofurans.
- The reported structure of the adducts should be revised.
- The actual structure was revealed from the ^{1}HNMR spectrum of the corresponding alcohols.