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Indoloquinones, Part 5.[1]

Palladium-Catalyzed Total Synthesis of the Potent Lipid Peroxidation Inhibitor Carbazoquinocin C

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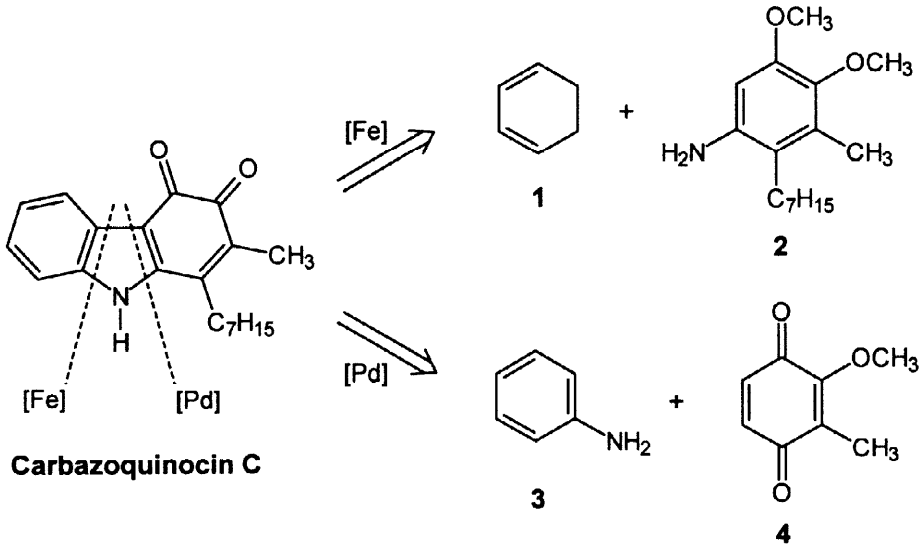
Abstract: The efficient palladium-catalyzed oxidative coupling of an anilinoquinone and subsequent regioselective introduction of the heptyl side chain provide the antioxidative substance carbazoquinocin C in four steps and 36% overall yield from aniline.

Over the past decades many biologically active carbazole alkaloids were obtained from terrestrial plants, marine sources, and streptomyces.[2] Their isolation induced the development of novel strategies for the total synthesis of structurally unprecedented carbazole derivatives.[3] Several of the carbazole alkaloids isolated from streptomyces exhibit an antioxidative activity.[4-5] These compounds are considered to represent potential therapeutic agents against a variety of diseases initiated by oxygen-derived free radicals, like myocardial and cerebral ischemia, arteriosclerosis, inflammation, rheumatism, senility, autoimmune diseases, and cancer.[6] Three years ago, Seto *et al.* isolated the carbazoquinocins from *Streptomyces violaceus* 2448-SVT2.[5] They showed strong inhibitory activity against lipid peroxidation and therefore, attracted the interest of synthetic chemists.[7-10]



Scheme 1

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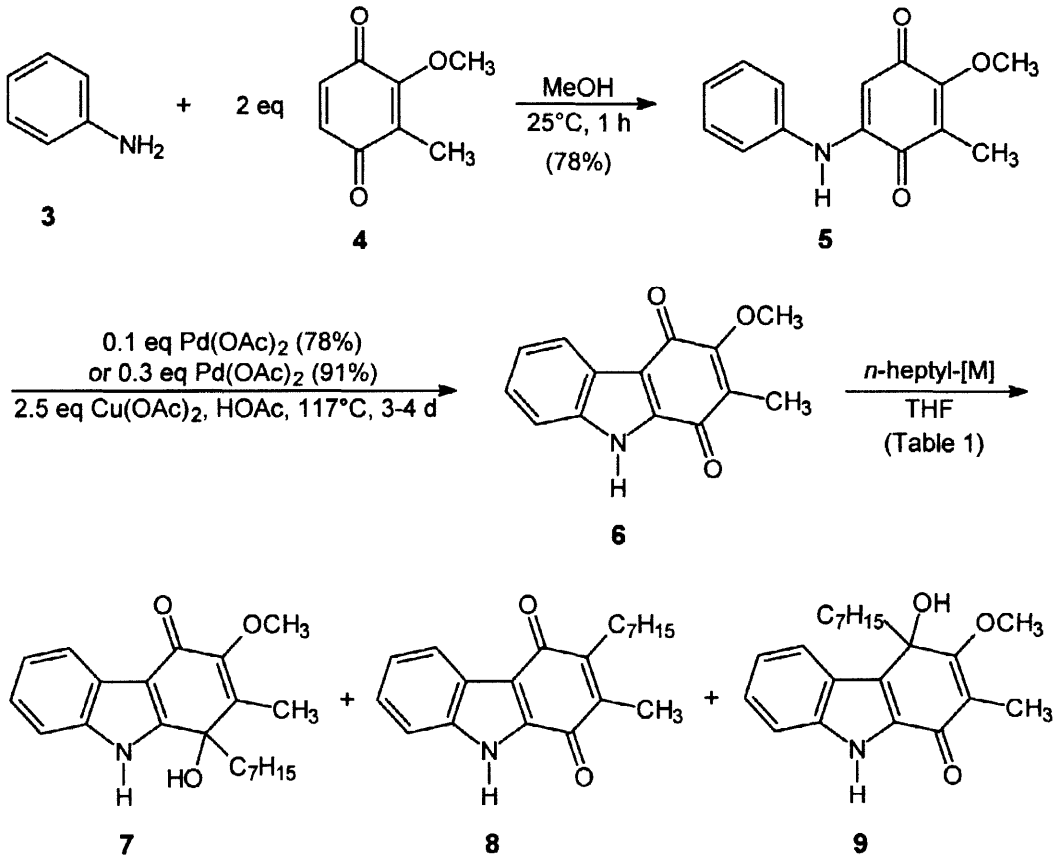
The total synthesis of the carbazoquinocins A and D was reported by Ogasawara.[7] We described a highly convergent synthesis of carbazoquinocin C *via* a one-pot construction of the carbazole framework[9] and Hibino prepared the carbazoquinocins B-F using an electrocyclic reaction of an appropriate allene intermediate.[10] Our first total synthesis of carbazoquinocin C was achieved by an iron-mediated oxidative coupling of cyclohexa-1,3-diene **1** and the fully functionalized arylamine **2** (Scheme 1).[9] In the present paper we report a novel synthesis of carbazoquinocin C starting from aniline **3** and the benzo-1,4-quinone **4** *via* the efficient palladium(II)-catalyzed oxidative cyclization of an intermediate anilinobenzoquinone as key-step.

The palladium-mediated cyclization of *N,N*-diarylamines originally reported by Åkermark represents a highly convergent route to carbazoles.[11] Application of this method to the cyclization of 2-anilinobenzo-1,4-quinones provided carbazole-1,4-quinones.[12] However, these oxidative cyclizations to carbazole derivatives required stoichiometric amounts of palladium(II) acetate, since one equivalent of palladium(0) is generated in the final reductive elimination. For the development of a catalytic reaction an *in situ* reoxidation of palladium(0) to palladium (II) is required.[13] The feasibility to achieve a catalytic cyclization of anilinoquinones by reoxidation of palladium with cupric acetate was demonstrated first by our earlier study reporting the synthesis of benzo[*b*]carbazole-6,11-diones.[14] This method was applied to an efficient palladium-catalyzed synthesis of the alkaloids carbazomycin G and H.[1] An alternative catalytic cyclization of anilinobenzoquinones by reoxidation of palladium with *tert*-butyl hydroperoxide was described by Åkermark.[15]



Scheme 2

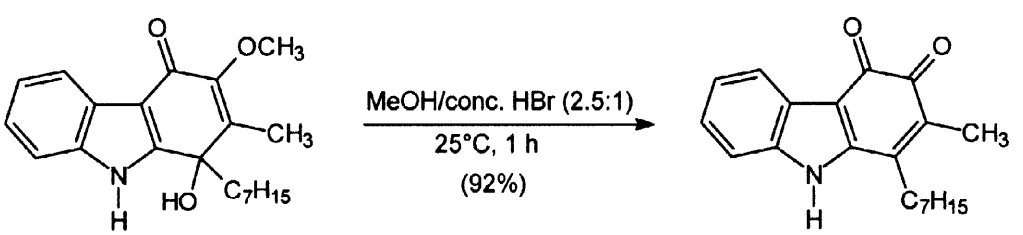
Reaction of aniline **3** with two equivalents of the 1,4-benzoquinone **4** afforded exclusively the anilinobenzoquinone **5** resulting from amine addition at C-5.[1,16] The palladium-catalyzed oxidative cyclization of compound **5**

to 3-methoxy-2-methylcarbazole-1,4-quinone **6**, previously used for the synthesis of carbazomycin G,[1] was improved (Scheme 2). The reaction was carried out in glacial acetic acid at reflux for 3-4 d in the air using 250 mol% of cupric acetate for the reoxidation of palladium. With 10 mol% of palladium(II) acetate as catalyst the carbazole-1,4-quinone **6** was obtained in 78% yield, using 30 mol% of the catalyst the product could be isolated in 91% yield. By this procedure large quantities of the crucial carbazole alkaloid precursor **6** became available.

Table 1. Results of the nucleophilic addition of *n*-heptylmetal reagents to the carbazole-1,4-quinone **6**.

n-heptyl-[M] (eq)	reaction conditions	**7**, Yield [%]	**8**, Yield [%]	**9**, Yield[%]
$C_7H_{15}Li$ (7.5)	-78°C, 2 h	33	66	trace
$C_7H_{15}MgCl$ (10.5)	-78°C, 0.5 h; 25°C, 17 h	43	23	31
$C_7H_{15}MgCl$ (15)	-78°C, 3 h	55	8	trace

The regioselective introduction of the heptyl side chain was the next important step in the palladium-catalyzed synthesis of carbazoquinocin C in contrast to the more convergent iron-mediated synthesis which started from a fully functionalized arylamine (*cf.* Scheme 1). The 1,2-addition at C-4 was thought to be disfavored because of the more deactivating effect of the vinylogous amide resonance contribution compared to the vinylogous ester resonance of the carbonyl group at C-1. This expectation was previously confirmed by the addition of methyl lithium at C-1 of compound **6** leading to carbazomycin G (71% yield).[1,17] However, addition of heptyl lithium at –78°C provided quantitatively the carbazolequinol **7** and 3-heptyl-2-methylcarbazole-1,4-quinone **8** (product of vinylogous addition) in a ratio of 1:2 (Scheme 2, Table 1). Reaction with heptylmagnesium chloride first at –78°C for 0.5 h and then at room temperature for 17 h afforded the desired carbazolequinol **7** in 43% yield along with the quinone **8** (23% yield) and the regioisomeric carbazolequinol **9** (31% yield), formed by 1,2-addition at C-4. The best result in favor of the 1,2-addition at C-1 of quinone **6** was obtained by addition of heptylmagnesium chloride at –78°C followed by reaction for 3 h at the same temperature which provided the carbazolequinole **7** in 55% yield. The structural assignment of the carbazolequinol **7** required for the total synthesis of carbazoquinocin C was based on a comparison of its UV spectrum and characteristic ^{1}H-NMR and ^{13}C-NMR data[18] with those of synthetic[1,17] and natural[19] carbazomycin G.



7 **Carbazoquinocin C**

Scheme 3

Finally, treatment of the carbazolequinol **7** with concentrated hydrogen bromide in methanol resulted in smooth conversion to carbazoquinocin C.

The present synthesis affords carbazoquinocin C in four steps and 36% overall yield based on **3**. All spectral data (UV, IR, ^{1}H-NMR, ^{13}C-NMR) of the synthetic carbazoquinocin C (m.p. 227-228°C) are in good agreement with those reported by Seto *et al.* for the natural product[5] (ref.[5]: m.p. 210-212°C; ref.[10]: m.p. 227-229°C).

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18. Carbazolequinol **7**: light yellow crystals, m.p. 174-176°C; UV (MeOH): λ = 212, 253, 277, 342 nm; IR (drift): ν = 3186, 2928, 2857, 1640, 1619, 1499, 1475, 1454, 1403, 1377, 1322, 1298, 1186, 1152, 1137, 1122, 1103, 1051, 1012, 880, 806, 744 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 0.59 (m, 1 H), 0.76 (t, J = 7.2, 3 H), 0.86 (m, 1 H), 1.05-1.16 (m, 8 H), 2.02 (s, 3 H), 2.04 (dt, J = 4.7, 12.6, 1 H), 2.13 (dt, J = 4.7, 12.6, 1 H), 3.71 (s, 3 H), 4.25 (br s, 1 H), 7.08 (br t, J = 7.5, 1 H), 7.13 (dt, J = 1.1, 7.5, 1 H), 7.30 (d, J = 7.5, 1 H), 7.93 (d, J = 7.5, 1 H), 9.80 (br s, 1 H); ^{13}C-NMR and DEPT (125 MHz, $CDCl_3$): δ = 10.05 (CH_3), 13.97 (CH_3), 22.47 (CH_2), 23.46 (CH_2), 28.88 (CH_2), 29.24 (CH_2), 31.61 (CH_2), 40.22 (CH_2), 60.14 (CH_3), 71.90 (C), 111.46 (C), 111.60 (CH), 121.18 (CH), 122.33 (CH), 123.75 (CH, C), 136.31 (C), 139.57 (C), 149.91 (C), 152.13 (C), 179.04 (C=O); MS (125°C): *m/z* (%) = 341 (M^+, 14), 325 (4), 310 (4), 242 (100), 199 (6); Anal. calcd. for $C_{21}H_{27}NO_3$: C 73.87, H 7.97, N 4.10; found: C 73.53, H, 7.90, N 4.06.
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