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Transition Metal Complexes in Organic Synthesis, Part 37.[1]

Convergent Iron-Mediated Total Synthesis of the Potent Lipid Peroxidation Inhibitor Carbazoquinocin C

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Abstract: The antioxidative agent carbazoquinocin C has been synthesized by a convergent iron-mediated construction of the carbazole nucleus using a novel one-pot C–C and C–N bond formation which is carried out in the air.

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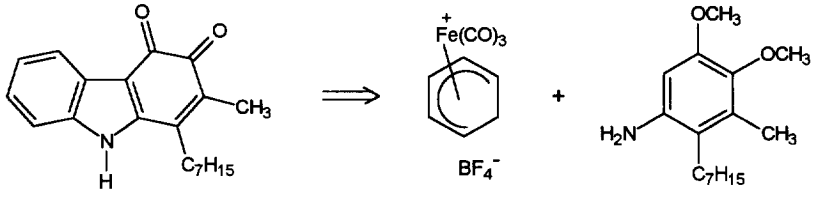
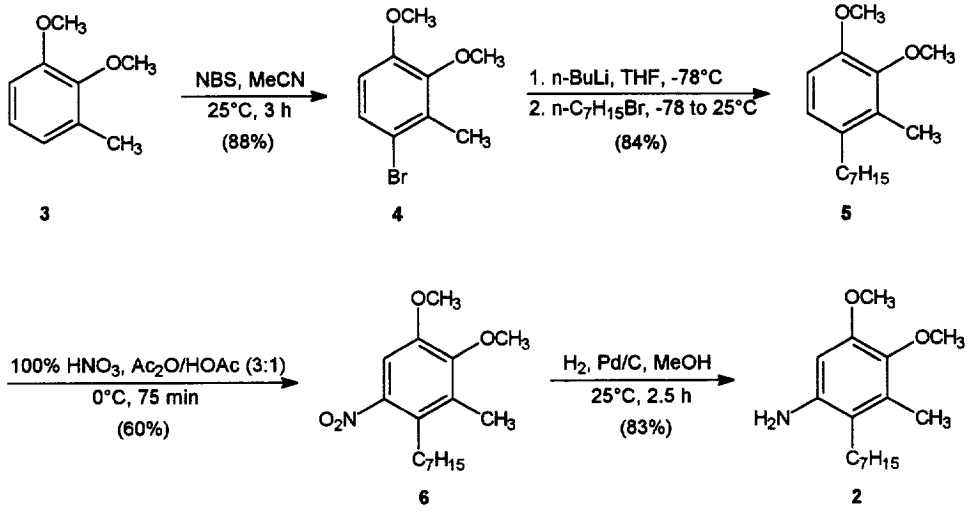
It is known that oxygen-derived free radicals play a central role in the initiation of a variety of diseases, like myocardial and cerebral ischemia, arteriosclerosis, inflammation, rheumatism, senility, autoimmune diseases, and cancer.[2] Therefore, antioxidative agents are considered to be potential protective agents against these diseases. Recently, Seto and coworkers isolated the carbazoquinocins A to F from *Streptomyces violaceus* 2448-SVT2.[3] These compounds represent a novel class of carbazole *ortho*-quinone alkaloids and exhibit a strong inhibitory activity against lipid peroxidation induced by free radicals. The isolation, structure elucidation, and the development of novel methodologies for the total synthesis of biologically active carbazole alkaloids have been a research area of increasing interest over the past years.[4] We developed convergent total syntheses of carbazole alkaloids by using transition metal-mediated reactions for the construction of the carbazole nucleus.[5,6] Because of the useful biological activities the carbazoquinocins are of high interest and represent promising targets for organic synthesis. Recent work by Ogasawara[7] described the first total synthesis of carbazoquinocin A and D and Hibino[8] reported a synthetic approach to the carbazoquinocins. We now describe the total synthesis of carbazoquinocin C based on the iron-mediated construction of the carbazole framework as the crucial step (Scheme 1). With this application to the synthesis of carbazoquinocin C we introduce for the first time a novel feature of our iron-mediated route to carbazole derivatives: the electrophilic aromatic substitution of the fully functionalized arylamine **2** with the iron complex salt **1** on reaction at room temperature in the air. Using these reaction conditions, the corresponding tricarbonyliron-complexed 4a,9a-dihydro-9*H*-carbazole is provided in high yield by a one-pot C–C and C–N bond formation.



Carbazoquinocin C **1** **2**

Scheme 1

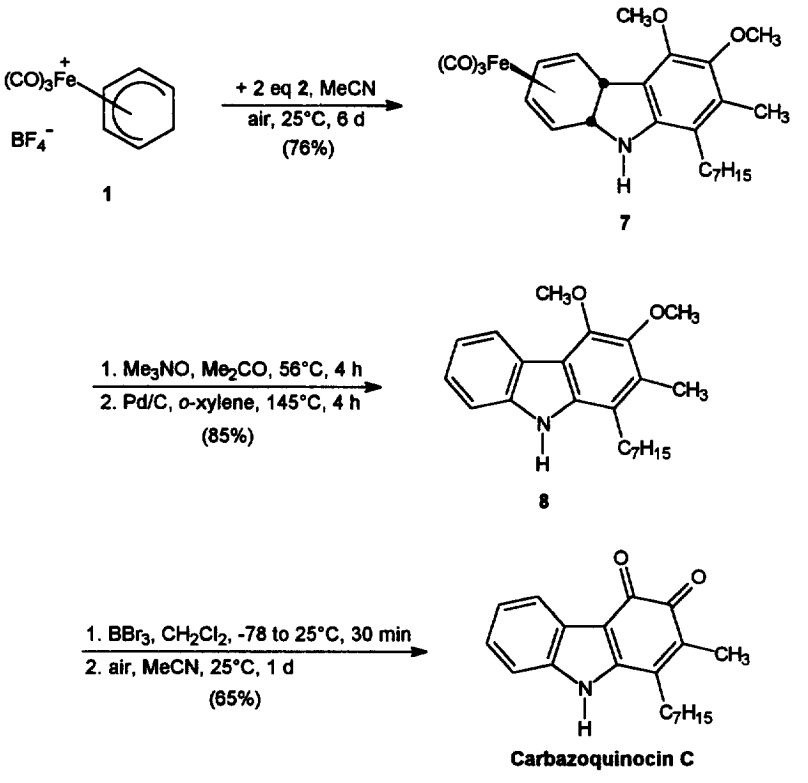
The required precursor **2** was prepared in a straightforward manner from commercial 2,3-dimethoxytoluene **3** (Scheme 2). Bromination of **3** with *N*-bromosuccinimide afforded regioselectively the 6-bromo derivative **4**.[9] Halogen/metal exchange using *n*-butyllithium followed by alkylation with 1-bromoheptane provided the heptyl derivative **5**. Nitration of **5** with fuming nitric acid in a mixture of acetic anhydride and glacial acetic acid (3:1) gave regioselectively the nitro derivative **6**. Evidence for the desired regioselectivity at this stage derived from comparison with literature known compounds.[10] Finally, hydrogenation of the nitro derivative **6** over 10% of palladium on activated carbon provided the required arylamine **2**. By this sequence the precursor **2** is available on a multigram scale in four steps and 37% overall yield.



Scheme 2

We recently reported that oxidative cyclizations of arylamine-substituted tricarbonyl(η^4-cyclohexa-1,3-diene)-iron complexes providing selectively the corresponding tricarbonyliron-complexed 4a,9a-dihydro-9*H*-carbazole derivatives are achieved simply by oxidation in the air with molecular oxygen in the presence of acid.[1] We now considered to combine this novel selective air-oxidation of the iron-complexed carbazole precursors with the electrophilic aromatic substitution affording the iron complexes. The acidic reaction conditions required for the air-oxidation would be provided by the tetrafluoroboric acid generated in the first step. In consequence, this procedure would provide a one-pot C–C and C–N bond formation furnishing directly the complete carbazole skeleton.

Reaction of the iron complex salt **1** with two equivalents of the arylamine **2** in acetonitrile at room temperature in the air provided after 6 days the tricarbonyl(η^4-4a,9a-dihydro-9*H*-carbazole)iron complex **7** in 76% yield.[11] The reactivity of these iron complexes and their transformation into the aromatized 9*H*-carbazoles was extensively investigated by us in our previous studies.[12] Thus, demetalation of complex **7** using trimethylamine *N*-oxide[13] in acetone at reflux and subsequent aromatization by catalytic dehydrogenation with 10% palladium on activated carbon in boiling *o*-xylene afforded 1-heptyl-3,4-dimethoxy-2-methylcarbazole **8** in 85% yield.[11] Ether cleavage of **8** with boron tribromide followed by oxidation at room temperature in the air provided carbazoquinocin C.



Scheme 3

All spectral data (UV, IR, ^{1}H-NMR, ^{13}C-NMR)[11] of our synthetic carbazoquinocin C (m.p. 211-212°C) are in good agreement with those reported for the natural product (m.p. 210-212°C).[3] The present synthesis provides carbazoquinocin C in five steps and an overall yield of 42% based on the iron complex salt **1**.

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11. Selected spectral data of the synthetic intermediates **7** and **8** and of the synthetic carbazoquinocin C.
Complex 7: IR (KBr): ν = 3396, 2927, 2859, 2043, 1975, 1931, 1601 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 0.89 (m, 3 H), 1.29-1.42 (m, 10 H), 2.12 (s, 3 H), 2.28-2.34 (m, 2 H), 3.19 (t, *J* = 4.5, 1 H), 3.31 (br s, 1 H), 3.68-3.70 (m, 1 H), 3.71 (s, 3 H), 3.89 (s, 3 H), 3.93 (dd, *J* = 10.7, 4.0, 1 H), 4.31 (dd, *J* = 10.7, 3.4, 1 H), 5.36 (m, 1 H), 5.40 (m, 1 H); ^{13}C-NMR and DEPT (125 MHz, $CDCl_3$): δ = 11.74 (CH_3), 14.13 (CH_3), 22.67 (CH_2), 28.30 (CH_2), 28.88 (CH_2), 29.25 (CH_2), 30.00 (CH_2), 31.91 (CH_2), 44.97 (CH), 60.22 (CH_3), 60.45 (CH_3), 61.44 (CH), 62.85 (CH), 63.30 (CH), 85.41 (CH), 86.57 (CH), 118.56 (C), 122.01 (C), 129.98 (C), 143.94(C), 144.07 (C), 146.99 (C), 211.37 (3 CO).
Carbazole **8**: UV (MeOH): λ = 220, 242, 261 (sh), 292, 327, 340 nm; IR (KBr): ν = 3344, 2926, 2855, 1611, 1502, 1456, 1401, 747 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.0, 3 H), 1.25-1.36 (m, 6 H), 1.43 (m, 2 H), 1.62 (quint, *J* = 8.0, 2 H), 2.38 (s, 3 H), 2.80 (t, *J* = 8.0, 2 H), 3.89 (s, 3 H), 4.10 (s, 3 H), 7.20 (m, 1 H), 7.34-7.39 (m, 2 H), 7.82 (br s, 1 H), 8.22 (d, *J* = 7.8, 1 H); ^{13}C-NMR and DEPT (125 MHz, $CDCl_3$): δ = 12.22 (CH_3), 14.10 (CH_3), 22.68 (CH_2), 28.65 (CH_2), 29.32 (CH_2), 29.54 (CH_2), 30.01 (CH_2), 31.87 (CH_2), 60.44 (CH_3), 60.95 (CH_3), 110.20 (CH), 114.62 (C), 118.82 (C), 119.39 (CH), 122.50 (CH), 122.84 (C), 125.02 (CH), 128.35 (C), 136.11 (C), 139.31 (C), 144.54 (C), 146.01 (C).
Carbazoquinocin C: m.p. 211-212°C; UV (MeOH): λ = 228, 265, 401 nm; IR (KBr): ν = 3216, 2927, 2856, 1640, 1627, 1467, 1249, 752 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 0.85 (t, *J* = 6.8, 3 H), 1.24-1.34 (m, 6 H), 1.44 (m, 2 H), 1.54 (m, 2 H), 1.89 (s, 3 H), 2.64 (t, *J* = 7.8, 2 H), 7.23 (m, 2 H), 7.49-7.51 (m, 1 H), 7.84-7.86 (m, 1 H), 12.32 (br s, 1 H); ^{13}C-NMR and DEPT (125 MHz, DMSO-d_6): δ = 11.45 (CH_3), 13.94 (CH_3), 22.06 (CH_2), 28.06 (CH_2), 28.52 (CH_2), 28.62 (CH_2), 29.00 (CH_2), 31.25 (CH_2), 111.04 (C), 113.37 (CH), 120.26 (CH), 123.95 (CH), 124.17 (CH), 125.66 (C), 133.10 (C), 137.06 (C), 142.12 (C), 145.62 (C), 172.72 (C=O), 183.46 (C=O).
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