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Transition Metal Complexes in Organic Synthesis, Part 36.[1] Cyclization of Tricarbonyliron Complexes by Oxygen to 4a,9a-Dihydro-9*H*-carbazoles: Application to the Synthesis of Mukonine, Mukonidine, and Pyrido[3,2,1-*jk*]carbazoles

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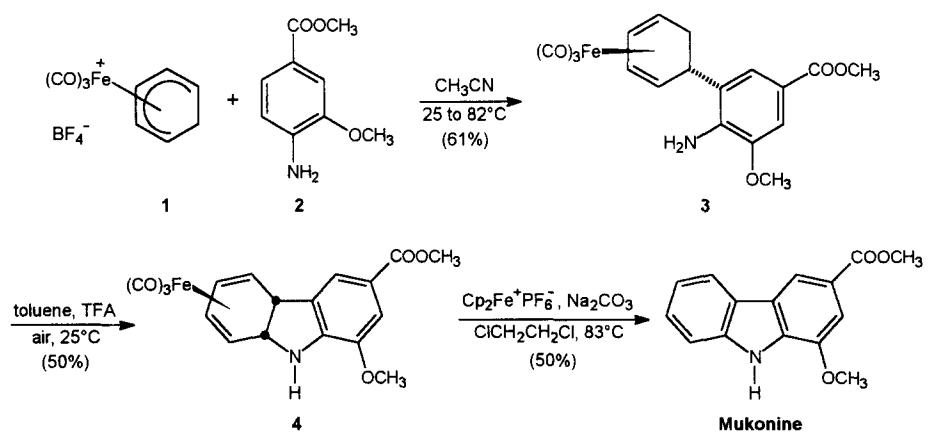
Abstract: Aryl-substituted tricarbonyl(η^4-cyclohexa-1,3-diene)iron complexes are oxidatively cyclized in protic medium in the air to tricarbonyliron-complexed 4a,9a-dihydro-9*H*-carbazoles. The method is applied to the total synthesis of mukonine and mukonidine.

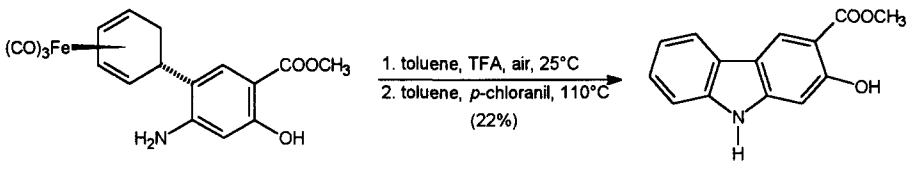
A broad range of biologically active carbazole alkaloids have been isolated from natural sources.[2] In the course of our ongoing project directed towards synthetic approaches to these natural products we described several tricarbonyliron-mediated syntheses.[3] The cyclizations of the intermediate aryl-substituted tricarbonyl(η^4-cyclohexa-1,3-diene)iron complexes were achieved with appropriate oxidizing agents, *e.g.* very active manganese dioxide, iodine, or ferricenium hexafluorophosphate, providing either directly the aromatized 9*H*-carbazoles or the intermediate tricarbonyliron-complexed 4a,9a-dihydro-9*H*-carbazoles.[1,4] We now report a novel cyclization to the 4a,9a-dihydro-9*H*-carbazole complexes by oxidation with molecular oxygen in presence of acid.[5]



Scheme 1

The application of this novel cyclization technique to the total synthesis of the alkaloid mukonine,[6] previously obtained by cyclization with manganese dioxide,[7] is shown in Scheme 1. An optimized procedure for the reaction of the complex salt **1** with the arylamine **2** provided complex **3** in 61% yield. Stirring of a solution of **3** in toluene with trifluoroacetic acid in the air resulted in smooth cyclizing dehydrogenation and afforded the tricarbonyl(4a,9a-dihydro-9*H*-carbazole)iron complex **4**. Aromatization of **4** with concomitant demetalation to mukonine was achieved by oxidation with ferricenium hexafluorophosphate in presence of sodium bicarbonate.

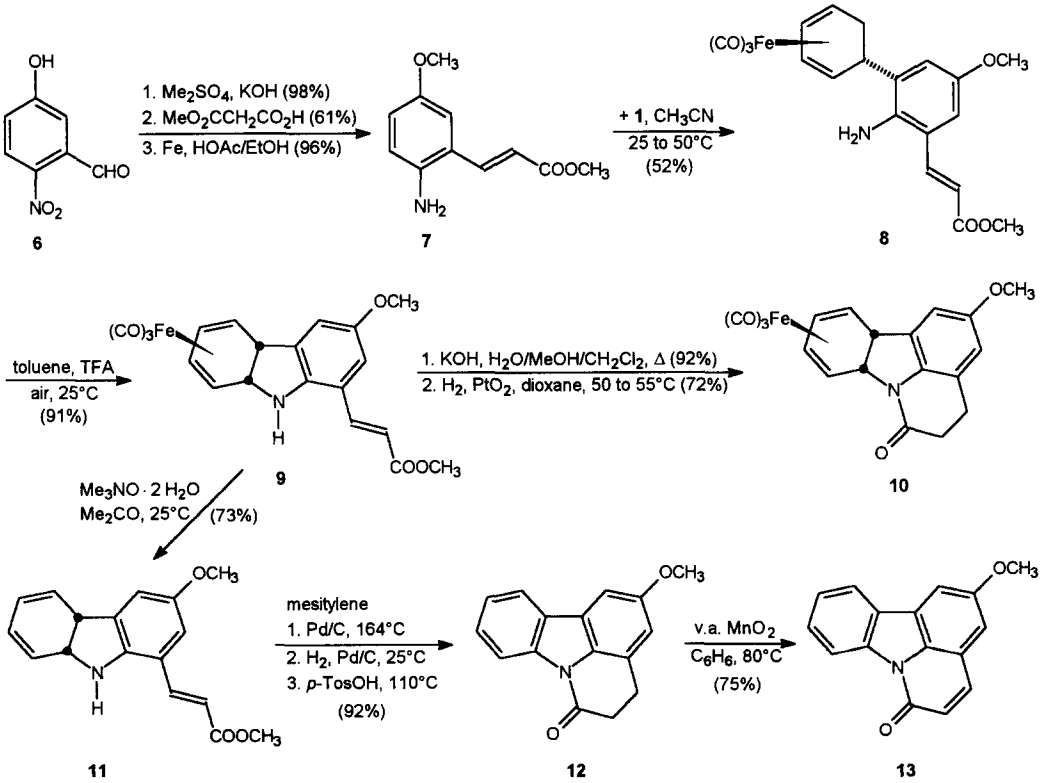
The isolation of mukonidine (methyl 2-hydroxycarbazole-3-carboxylate) was claimed by Chakraborty from *Murraya koenigii*[8] and by Wu from *Clausena excavata*.[9] However, the spectral data and the melting points for both natural products were not in agreement and therefore, one of them must have a different structure.[10] In order to solve this problem we envisaged a total synthesis of mukonidine. Previous attempts *via* tricarbonyliron complexes[11] and using a molybdenum-mediated approach[12] were unsuccessful. Cyclization of complex **5**[11] with air in toluene/TFA at room temperature afforded the corresponding dihydrocarbazole complex which was *in situ* aromatized and demetalated by refluxing in toluene with *p*-chloranil to give mukonidine (Scheme 2).



5 **Mukonidine**

Scheme 2

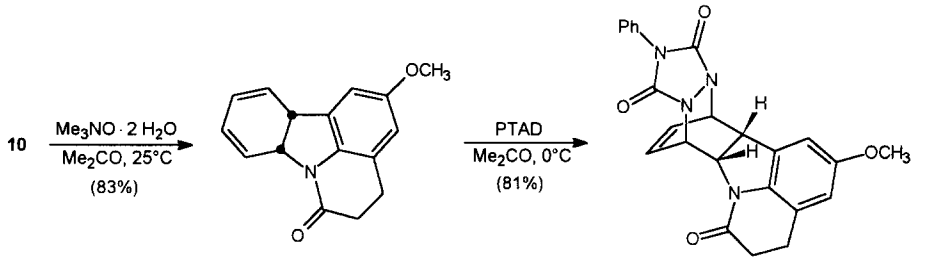
The spectral data (UV, IR, ^{1}H-NMR, and MS)[13] of our synthetic mukonidine (colorless crystals, m.p. 190°C) are in good agreement with those reported for the natural product by Wu (m.p. 168-170°C).[9] Whereas the melting point is in better agreement with that reported by Venkataraman (m.p. 188°C).[10b] It is therefore concluded that the structure of the natural product isolated by Chakraborty (m.p. 245°C)[8] may be different.



6 **7** **8** **9** **10** **11** **12** **13**

Scheme 3

For a projected synthesis of indole alkaloid derivatives we devised an iron-mediated route to the pyrido[3,2,1-*jk*]carbazole framework (Scheme 3). 2-Nitro-5-hydroxybenzaldehyde **6** was transformed into methyl 2-amino-5-methoxycinnamate **7** by modification of a literature procedure.[14] Electrophilic substitution of **7** by the iron complex salt **1** afforded regio- and stereoselectively the complex **8**. Bubbling of air through a stirred solution of complex **8** in toluene/trifluoroacetic acid (15:1) led to a selective cyclizing dehydrogenation and provided the tricarbonyl(4a,9a-dihydro-9*H*-carbazole)iron complex **9** in 91% yield. Cleavage of the ester and subsequent hydrogenation of the double bond enabled cyclization to the tricarbonyliron-complexed tetracyclic lactam **10**. Alternatively, the desired pyrido[3,2,1-*jk*]carbazole ring system was constructed by aromatization prior to lactamization. Demetalation of **9** with trimethylamine *N*-oxide[15] gave the deliberated free ligand **11** in 73% yield. Aromatization of **11** with palladium on carbon followed by hydrogenation of the double bond and cyclization with *p*-toluenesulfonic acid in mesitylene at reflux afforded the aromatized tetracyclic lactam **12** in 92% overall yield.[16] Dehydrogenation with very active manganese dioxide[17] provided 2-methoxy-6*H*-pyrido[3,2,1-*jk*]carbazol-6-one **13**.



Scheme 4

Smooth demetalation of the iron-complexed lactam **10** with trimethylamine *N*-oxide[15] afforded in 83% yield the dihydro derivative **14** which exhibited useful reactivity in further transformations.[5] First, dehydrogenation with palladium on carbon opens up an alternative route to the aromatized tetracyclic lactam **12**. Second, the stereoselectivity of reactions at the cyclohexadiene moiety was shown by a 1-aza-1,3-butadiene-catalyzed[18] recomplexation of **14** with nonacarbonyldiiron in glyme at reflux. This reaction afforded in 87% yield complex **10** with the original stereochemistry resulting from approach of the tricarbonyliron fragment from the convex face and represents a further example of the complete *exo*-selectivity in reactions of annulated cyclohexadienes incorporated in a carbazole framework. Third, the stereoselective Diels-Alder cycloaddition of **14** with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD)[19] provided compound **15** in 81% yield. The stereochemistry was assigned based on analogy with the *exo*-selective $Fe(CO)_3$-recomplexation.

In conclusion, we could demonstrate that methoxycarbonyl-substituted hydroxy- and methoxyanilines can be converted to the corresponding tricarbonyl(4a,9a-dihydro-9*H*-carbazole)iron complexes by a two-step process on reaction with the complex salt **1** without using strong oxidizing agents. The transformation involves C–C bond formation by regioselective electrophilic substitution of the *ortho*-amino position and subsequent C–N bond formation by oxygen-mediated cyclization of the resulting iron complex in acidic toluene solution.

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13. **Mukonidine**: Colorless crystals, m.p. 190°C; UV (EtOH): λ = 191, 231, 235, 243, 284, 325, 338 nm; IR (KBr): ν = 3355, 1647, 1632, 1466, 1435, 1376, 1240, 1168, 1097, 1016, 951, 899, 872, 823, 786, 764, 722, 700 cm^{-1}; ^{1}H-NMR (400 MHz, CD_3COCD_3): δ = 3.98 (s, 3 H), 6.93 (s, 1 H), 7.19 (t, J = 7.7 Hz, 1 H), 7.36 (t, J = 8.1 Hz, 1 H), 7.46 (d, J = 8.1 Hz, 1 H), 8.06 (d, J = 7.7 Hz, 1 H), 8.59 (s, 1 H), 10.50 (br s, 1 H), 11.10 (s, 1 H); ^{13}C-NMR and DEPT (100 MHz, CD_3COCD_3): δ = 53.17 (CH_3), 98.26 (CH), 106.50 (C), 112.36 (CH), 118.40 (C), 121.15 (CH), 121.45 (CH), 123.97 (CH), 124.87 (C), 127.06 (CH), 142.51 (C), 147.17 (C), 162.18 (C), 172.78 (C=O); MS (95°C): *m/z* (%) = 241 (M^+, 52), 210 (17), 209 (100), 208 (6), 181 (13), 154 (6), 153 (24), 126 (6); HRMS: Calcd. for $C_{14}H_{11}NO_3$: 241.0739, found: 241.0729.
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