

Transition Metal Complexes in Organic Synthesis, Part 36.¹

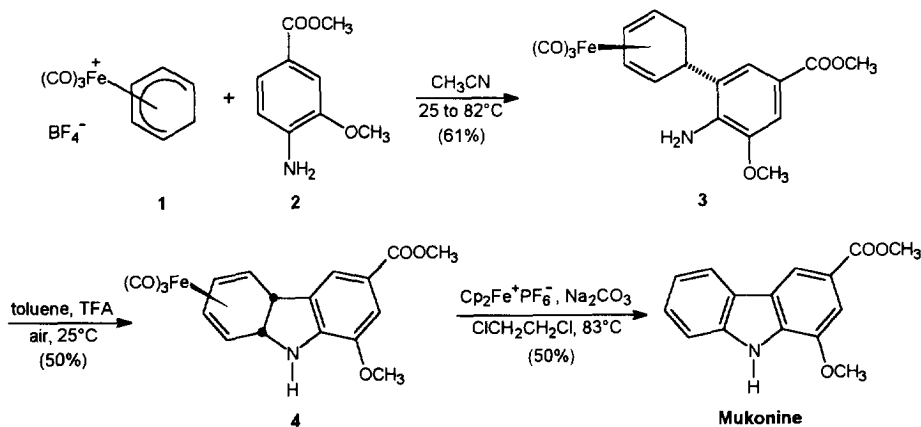
Cyclization of Tricarbonyliron Complexes by Oxygen to 4a,9a-Dihydro-9H-carbazoles: Application to the Synthesis of Mukonine, Mukonidine, and Pyrido[3,2,1-*jk*]carbazoles

*Hans-Joachim Knölker** and *Marcus Wolpert*

Institut für Organische Chemie, Universität Karlsruhe, Richard-Willstätter-Allee, 76131 Karlsruhe, Germany

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-9H-carbazoles. The method is applied to the total synthesis of mukonine and mukonidine.
 © 1997, Elsevier Science Ltd. All rights reserved.

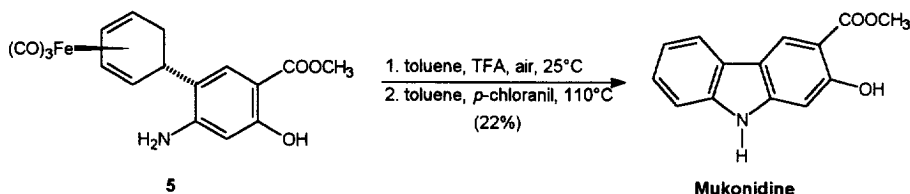
A broad range of biologically active carbazole alkaloids have been isolated from natural sources.² In the course of our ongoing project directed towards synthetic approaches to these natural products we described several tricarbonyliron-mediated syntheses.³ The cyclizations of the intermediate aryl-substituted 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 9H-carbazoles or the intermediate tricarbonyliron-complexed 4a,9a-dihydro-9H-carbazoles.^{1,4} We now report a novel cyclization to the 4a,9a-dihydro-9H-carbazole complexes by oxidation with molecular oxygen in presence of acid.⁵



Scheme 1

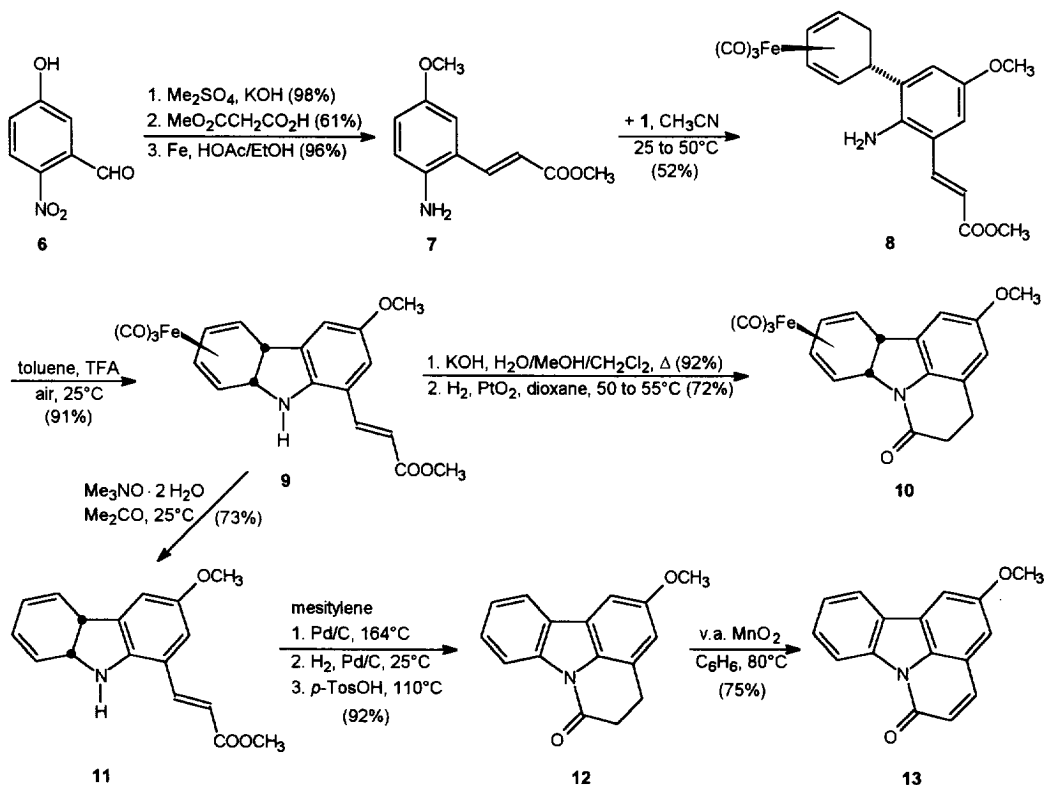
The application of this novel cyclization technique to the total synthesis of the alkaloid mukonine,⁶ previously obtained by cyclization with manganese dioxide,⁷ is shown in Scheme 1. An optimized procedure for the reaction of the complex salt 1 with the arylamine 2 provided complex 3 in 61% yield. Stirring 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-9H-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 complexes¹¹ and using a molybdenum-mediated approach¹² were unsuccessful. Cyclization of complex **5** 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).



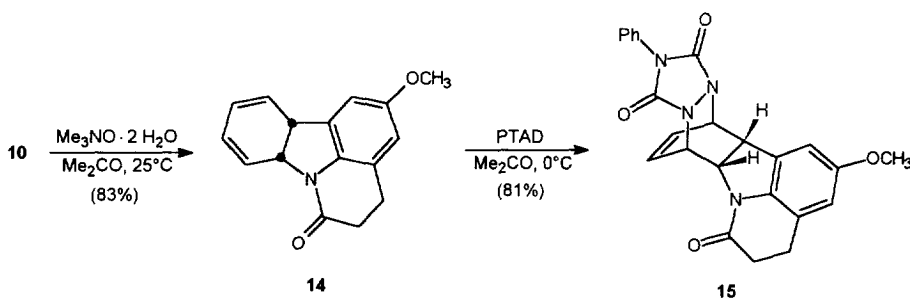
Scheme 2

The spectral data (UV, IR, ¹H-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.



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*-oxide¹⁵ 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 dioxide¹⁷ 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*-oxide¹⁵ 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-catalyzed¹⁸ recomplexation of **14** with nonacarbonyliron 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.

Acknowledgements: This work was supported by the Deutsche Forschungsgemeinschaft (Gerhard-Hess Award) and the Fonds der Chemischen Industrie.

References and Notes

1. Part 35: H.-J. Knölker, W. Fröhner, *Tetrahedron Lett.* **1996**, *37*, in print.
2. D. P. Chakraborty, S. Roy in *Prog. Chem. Org. Nat. Prod.*, Vol. 57 (Eds.: W. Herz, H. Grisebach, G. W. Kirby, C. Tamm), Springer, Wien, **1991**, p. 71; D. P. Chakraborty in *The Alkaloids*, Vol. 44 (Ed.: A. Brossi), Academic Press, New York, **1993**, p. 257.
3. Reviews: H.-J. Knölker in *Organic Synthesis via Organometallics* (Eds.: K. H. Dötz, R. W. Hoffmann), Vieweg, Braunschweig, **1991**, p. 119; H.-J. Knölker, *Synlett* **1992**, 371; H.-J. Knölker in *Advances in Nitrogen Heterocycles*, Vol. 1 (Ed.: C. J. Moody), JAI Press, Greenwich (CT), **1995**, p. 173.
4. H.-J. Knölker, M. Bauermeister, *Heterocycles* **1991**, *32*, 2443; H.-J. Knölker, M. Bauermeister, J.-B. Pannek, *Chem. Ber.* **1992**, *125*, 2783; H.-J. Knölker, M. Bauermeister, J.-B. Pannek, D. Bläser, R. Boese, *Tetrahedron* **1993**, *49*, 841; H.-J. Knölker, M. Bauermeister, *Helv. Chim. Acta* **1993**, *76*, 2500; H.-J. Knölker, E. Baum, T. Hopfmann, *Tetrahedron Lett.* **1995**, *36*, 5339; A. J. Birch, A. J. Liepa, G. R. Stephenson, *Tetrahedron Lett.* **1979**, 3565.
5. For previous work on the synthesis and reactions of 4a,9a-dihydro-9H-carbazoles, see: D. B. Grotjahn, K. P. C. Vollhardt, *J. Am. Chem. Soc.* **1986**, *108*, 2091; H.-J. Knölker, P. G. Jones, J.-B. Pannek, A. Weinkauff, *Synlett* **1991**, 241; H.-J. Knölker, G. Baum, J.-B. Pannek, *Tetrahedron* **1996**, *52*, 7345.
6. D. P. Chakraborty in *Prog. Chem. Org. Nat. Prod.*, Vol. 34 (Eds.: W. Herz, H. Grisebach, G. W. Kirby), Springer, Wien, **1977**, p. 299.
7. H.-J. Knölker, M. Bauermeister, *J. Chem. Soc. Chem. Commun.* **1990**, 664; H.-J. Knölker, M. Bauermeister, *Tetrahedron* **1993**, *49*, 11221.
8. D. P. Chakraborty, S. Roy, R. Guha, *J. Indian Chem. Soc.* **1978**, *55*, 1114.
9. T.-S. Wu, S.-C. Huang, J.-S. Lai, C.-M. Teng, F.-N. Ko, C.-S. Kuoh, *Phytochemistry* **1993**, *32*, 449.
10. In this context, see also: (a) P. Bhattacharyya, A. Chakraborty, *Phytochemistry* **1984**, *23*, 471; (b) M. R. R. Bhagwanth, A. V. Rama Rao, K. Venkataraman, *Indian J. Chem.* **1969**, *7*, 1065.
11. H.-J. Knölker, M. Bauermeister, *J. Indian Chem. Soc.* **1994**, *71*, 345.
12. H.-J. Knölker, H. Goesmann, C. Hofmann, *Synlett* **1996**, 737.
13. **Mukonidine**: Colorless crystals, m.p. 190°C; UV (EtOH): $\lambda = 191, 231, 235, 243, 284, 325, 338$ nm; IR (KBr): $\nu = 3355, 1647, 1632, 1466, 1435, 1376, 1240, 1168, 1097, 1016, 951, 899, 872, 823, 786, 764, 722, 700$ cm⁻¹; ¹H-NMR (400 MHz, CD₃COCD₃): $\delta = 3.98$ (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); ¹³C-NMR and DEPT (100 MHz, CD₃COCD₃): $\delta = 53.17$ (CH₃), 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 C₁₄H₁₁NO₃: 241.0739, found: 241.0729.
14. A. Galun, A. Markus, A. Kampf, *J. Heterocyclic Chem.* **1979**, *16*, 221; D. M. Fink, R. C. Allen, *Tetrahedron Lett.* **1992**, *33*, 2103.
15. Y. Shvo, E. Hazum, *J. Chem. Soc. Chem. Commun.* **1974**, 336; H.-J. Knölker, *J. Prakt. Chem.* **1996**, *338*, 190.
16. For a recent alternative synthesis of this ring system, see: J. H. Markgraf, M. Finkelstein, J. R. Cort, *Tetrahedron* **1996**, *52*, 461.
17. A. J. Fatiadi, *Synthesis* **1976**, 65; H.-J. Knölker, *J. Prakt. Chem.* **1995**, *337*, 75.
18. H.-J. Knölker, P. Gonser, *Synlett* **1992**, 517; H.-J. Knölker, P. Gonser, P. G. Jones, *Synlett* **1994**, 405.
19. J. Sauer, B. Schröder, *Chem. Ber.* **1967**, *100*, 678; C. J. Moody, *Adv. Heterocycl. Chem.* **1982**, *30*, 1.

(Received in Germany 20 November 1996; accepted 27 November 1996)