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Moore-Type Cyclization Leading to Arene Chromium Tricarbonyl 1,4-Diradical Intermediates and the Isolation of Indolines

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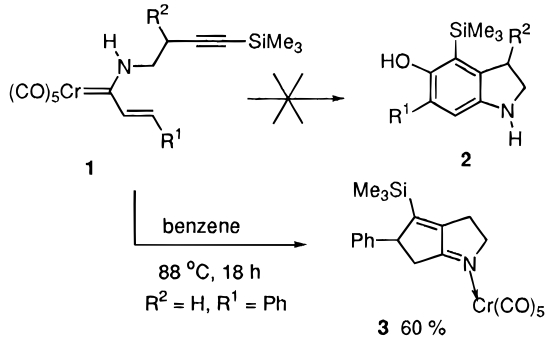
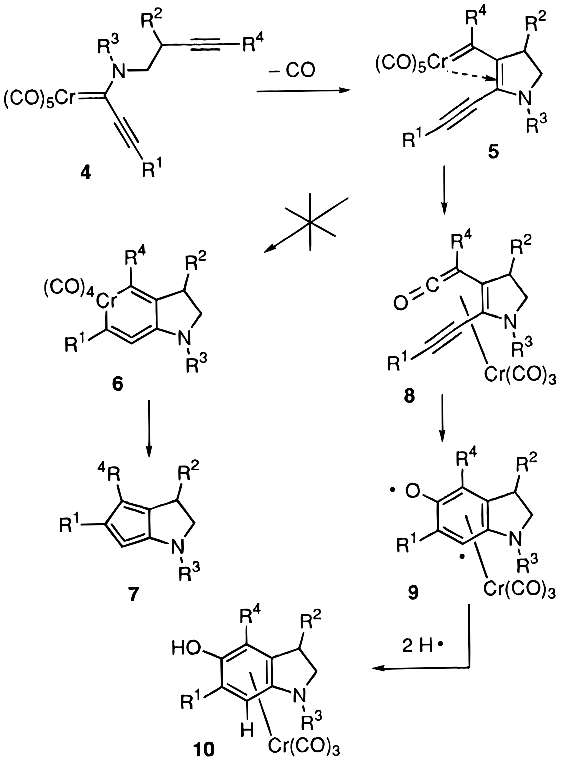
Compounds containing the 5-hydroxyindole unit are among the most active compounds in the central nervous system.[1] A convergent approach to this unit is possible on paper from the intramolecular benzannulation reaction of carbene complex **1** where both rings of the indoline unit are generated in a single step. It has long been known that the reactions of aryl amino carbene complexes with alkynes proceed to give five-membered-ring annulated products.[2] In contrast, it has recently been found that alkenyl amino complexes react with alkynes to produce six-membered-ring annulated products that contain a phenol function.[3] As a result of these observations, the intramolecular benzannulation of vinyl amino carbene complexes of the type **1** (Scheme 1) promised to provide a new and straightforward approach to the synthesis of 5-hydroxyindoles.[3] However, we have found that this will not be possible since, for example, thermolysis of complex **1** (R^2 = H, R^1 = Ph) produces the 1-azabicyclooctane **3** rather than the 5-hydroxyindoline **2**.[4]

It was reasoned that the failure of the thermolysis of complex **1** to give the indoline **2** was the result of the failure of a carbon monoxide insertion to compete with a cyclization on chromium to form a chromacyclohexadiene, which upon reductive elimination gives the observed five-membered ring. A solution to this problem was envisioned upon consideration of the cycloaromatization of enynyl ketenes that has recently been developed by Moore, Liebeskind, Nakatani, and Saito.[5] This cyclization gives phenols via a 1,4-diradical intermediate with one radical center on the phenol oxygen and the other at a meta position on the newly formed arene ring. As indicated in Scheme 2, it should be possible to set up this reaction with a chromium carbene complex if an alkynyl substituent is incorporated onto the carbene complex. The thermolysis of complex **4** would be expected to give an indoline product rather than the five-membered-ring product analogous to **3** since that pathway would require the cyclization of the intermediate **5** to give the species **6**, which contains an allene in a six-membered ring. We report here the success of this strategy for the synthesis of indolines in a process that involves the first example of a cycloaromatization reaction via 1,4-diradical intermediates where the newly formed arene ring is generated in the coordination sphere of a metal.[6]

Scheme 1



Scheme 2



The amino-tethered bis-alkynyl carbene complexes were prepared by aminolysis of the corresponding methoxyl complexes **11** with 1-amino-3-pentyne and then, without isolation, N-methylation to directly give the complexes **12** in good overall yields.[9] The thermolysis of the phenyl-substituted complex **12a** in the presence of 1,4-cyclohexadiene as a hydrogen source was examined under a variety of conditions. We were delighted to see that, as anticipated by the mechanism in Scheme 2, the generation and cyclization of an enynyl ketene intermediate to a 1,4-diradical intermediate did occur as evidenced by the isolation of the indoline **13a** (Scheme 3). However, the yields

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[1] (a) Hugel, H. M.; Kennaway, D. J. *Org. Prep. Proced. Int.* **1995**, *27*, 1. (b) Levy, A. D.; van de Kar, L. D. *Life Sci.* **1992**, *51*, 83. (c) Peroutka, S. J. *Pharmacol. Toxicol.* **1990**, *67*, 373. (d) Glennon, R. A. *J. Med. Chem.* **1987**, *30*, 1.

[2] (a) Yamashita, A. *Tetrahedron Lett.* **1986**, *27*, 5915. (b) For a list of subsequent examples, see ref 3.

[3] Wulff, W. D.; Gilbert, A. M.; Hsung, R. P.; Rahm, A. *J. Org. Chem.* **1995**, *60*, 4566.

[4] Rahm, A.; Wulff, W. D. *Tetrahedron Lett.* **1995**, *36*, 8753.

[5] (a) Foland, L. D.; Karlsson, J. O.; Perri, S. T.; Schwabe, R.; Xu, S. L.; Patil, S.; Moore, H. W. *J. Am. Chem. Soc.* **1989**, *111*, 975. (b) Xia, H.; Moore, H. W. *J. Org. Chem.* **1992**, *57*, 3765. (c) Sullivan, R. W.; Coghlan, V. M.; Munk, S. A.; Reed, M. W.; Moore, H. W. *J. Org. Chem.* **1994**, *59*, 2276. (d) Liebeskind, L. S.; Foster, B. S. *J. Am. Chem. Soc.* **1990**, *112*, 8612. (e) Nakatani, K.; Isoe, S.; Maekawa, S.; Saito, I. *Tetrahedron Lett.* **1994**, *35*, 605. This reaction is isoelectronic with the cycloaromatization of enynyl allenes that was originally reported by Myers: (f) Myers, A. G.; Kuo, E. Y.; Finney, N. S. *J. Am. Chem. Soc.* **1989**, *111*, 8057.

[6] A recent report describes a Bergman-type cyclization with the metal atom in a 10-membered ring containing an enediyne unit,[7] and another describes a Myers-type cyclization with an enyne-substituted vinylidene complex.[8]

[7] Warner, B. P.; Millar, S. P.; Broene, R. D.; Buchwald, S. L. *Science* **1995**, *269*, 814.

[8] Wang, Y.; Finn, M. G. *J. Am. Chem. Soc.* **1995**, *117*, 8045.

[9] The alkynyl (alkoxy) carbene complexes **11** were prepared by the method of Fischer,[10] and 1-amino-3-pentyne was isolated as its hydrochloride salt from a two-step sequence beginning with 4-hexynoic acid via the acid chloride in 72% yield by a Curtius rearrangement by the procedure of Nägeli where trimethylsilyl azide is substituted for sodium azide.[11] See supporting information for details.

[10] Complexes **11** were prepared according to procedures found in the following references, where in some cases methyl triflate was substituted as the methylating agent: (a) Fischer, E. O.; Kreissl, R. R. *J. Organomet. Chem.* **1972**, *35*, C47. (b) Chan, K. S.; Wulff, W. D. *J. Am. Chem. Soc.* **1986**, *108*, 5229.

[11] Möller, F. In *Methoden der Organischen Chemie (Houben-Weyl)*; Georg Thieme Verlag: Stuttgart, 1957; Vol. 11/1, p 865.

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Scheme 3

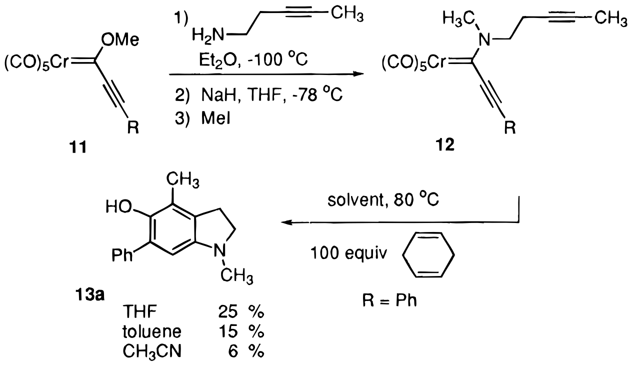
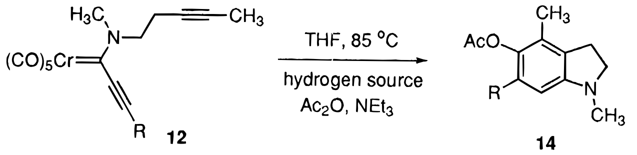


Table 1



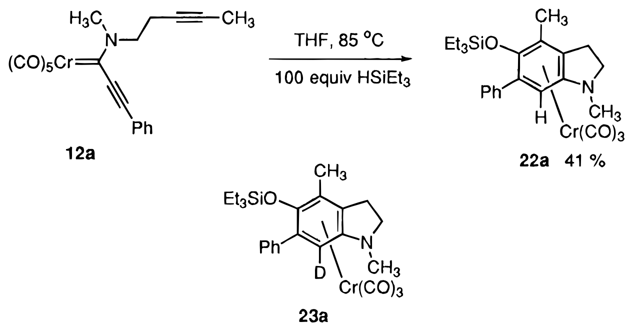
R	carbene complex[a]	% yield of **12**	hydrogen source (HS)	[**12**]	[HS]	% yield of **14**
Ph	**12a**	71	1,4-cyclohexadiene	0.005	0.5	43
Ph	**12a**	71	1,4-cyclohexadiene	0.01	0.1	34
Ph	**12a**	71	1,4-cyclohexadiene	0.01	1.0	63
Ph	**12a**	71	1,4-cyclohexadiene	0.02	2.0	49
Ph	**12a**	71	γ-terpinene	0.02	2.0	53
t-Bu	**12b**	66	γ-terpinene	0.02	2.0	31
SiMe$_3$	**12c**	70	γ-terpinene	0.02	2.0	ND[b]
1-C$_6$H$_9$	**12d**	68	γ-terpinene	0.02	2.0	41

[a] Complexes **12** were prepared as indicated in Scheme 3 and obtained as only the *E* isomer, except for **12c**, which was obtained as a 16:1 mixture of *E* and *Z* isomers; see ref 13. [b] Not detected.

for these cyclizations are low, giving a 25% yield of **13a** under the best conditions. The loss of the metal from the product is not surprising given the known air sensitivity of phenol chromium tricarbonyl complexes formed in the normal benzannulation reaction.[12]

In some instances it has been observed that the yields of benzannulated products can be improved if the reaction is carried out in the presence of electrophiles that are added to affect in situ protection of the phenol function.[12] As indicated by the data in Table 1, the yields of the indoline products could be greatly enhanced if the reaction was performed in the presence of acetic anhydride and triethylamine. The optimal conditions were found to be 0.01 M in THF at 80 °C with 100 equiv of 1,4-cyclohexadienone. Given the expense of the large excess of 1,4-cyclohexadiene required, a switch was made in hydrogen source to γ-terpinene, a naturally occurring 1,4-cyclohexadiene. Several reactions were screened with γ-terpinene at 0.02 M, and it was found that several different substituents on the alkynyl group could be tolerated and only the silylated complex **12c** failed to cyclize. It was unexpected to find that the cyclized products were isolated as metal-free compounds since (arene)-chromium tricarbonyl complexes are almost always isolated in cases where phenols are formed from the benzannulation of alkenyl carbene complexes with alkynes and trapped in situ, especially since this is also the case for intermolecular reactions of amino (alkenyl) carbene complexes.[3,12]

Scheme 4



If the metal is lost from the hydroxyindoline product **10** because the in situ protection of the phenol function is too slow, then, perhaps, it would be possible to prevent the loss of the metal by employing a trapping agent for the diradical intermediate **9** that would lead directly to a compound with a protected phenol function. Indeed, when the thermolysis of complex **12a** was carried out in the presence of triethylsilane, only the silylated 5-hydroxyindoline chromium tricarbonyl complex **22a** was isolated (Scheme 4). The isolation of metal complex **22a** indicates that the cyclization of the enynyl ketene to the diradical intermediate occurs in the coordination sphere of the metal. Proof of this would require demonstrating that the metal is not lost from the ketene complex **8** and then becomes recomplexed to the indoline product after its formation. While this has not been experimentally addressed here, it has been shown that the formation of (phenol)chromium tricarbonyl complexes from the benzannulation reaction of Fischer carbene complexes with alkynes occurs with the formation of the arene ring in the coordination sphere of the metal and without the loss of the metal at any time during during the reaction.[15] The thermolysis of **12a** in deuteriotriethylsilane gave the deuterated complex **23a**, which by deuterium NMR was found to have deuterium incorporated exclusively at the C-7 position. However, ^{1}H NMR revealed that the extent of deuterium incorporation at C-7 was only 25%, indicating that the solvent competes with the DSiEt$_3$ for the C-7 radical center. None of the metal-free 5-hydroxyindoline **13a** was observed, indicating that the oxygen radical at C-6 is apparently selectively silylated.

The new synthesis of 5-hydroxyindolines described herein is made possible by a metal-mediated Moore-type cyclization of an enynyl ketene complex and features the construction of both rings of the indole nucleus in a single step.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(12) (a) Chamberlin, S.; Wulff, W. D. *J. Am. Chem. Soc.* **1992**, *114*, 10667. (b) Chamberlin, S.; Wulff, W. D.; Bax, B. *Tetrahedron* **1993**, *49*, 5531.

(13) The carbene complexes **12** can exist as two diastereomers due to hindered rotation about the nitrogen–carbene carbon bond. The stereochemistry was assigned on the basis of the chemical shift of the methylene and methyl groups attached to the nitrogen atom and the observation that the closer a proton is to the metal center the greater the deshielding.[14] See supporting information for details.

(14) (a) Moser, E.; Fischer, E. O. *J. Organomet. Chem.* **1969**, *16*, 275. (b) Fischer, E. O.; Leupold, M. *Chem. Ber.* **1972**, *105*, 599. (c) Anderson, B. A.; Wulff, W. D.; Rahm, A. *J. Am. Chem. Soc.* **1993**, *115*, 4602.

(15) Dötz, K. H. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 644.