Novel Intramolecular Cycloaddition Reactions of Arylamino-Substituted Fischer Chromium Carbenes

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Received May 24, 1993[●]

Summary: Thermal reaction of *N*-arylamino-substituted Fischer chromium carbenes having a pendant 2-(1-alkenyl)substituent on the benzene ring affords either substituted indoles or quinolines, depending on starting material, via an intramolecular [2 + 2] cycloaddition forming a metallacyclobutane followed by metathesis to give indoles or β-elimination to give quinolines.

Fischer carbenes have been employed as starting material in several different cycloaddition reactions forming complex organic compounds. For example, synthesis of cyclobutanones[2] and β-lactams[3] by a formal [2 + 2] addition reaction with alkenes, fused polycyclic phenols by reaction of unsaturated carbenes with alkynes,[4] and cyclopropanes by reactions with alkenes[5] have all been reported. In addition to the more well-precedented reactions recent applications of cycloaddition reactions of Fischer carbenes include syntheses of hexahydroazulenes,[6] cyclopentenones,[7] aminobenzenes,[8] and pyrrolidines.[9]

It has previously been shown that upon irradiation of *N*-arylamino-substituted chromium carbenes under a carbon monoxide atmosphere and in the presence of alkenes α-amino-substituted cyclobutanones are formed in fair yield (Scheme I).[10] The reaction is thought to proceed via the formation of a metal-bound ketene intermediate, followed by intermolecular [2 + 2] addition to the alkene.

Scheme I

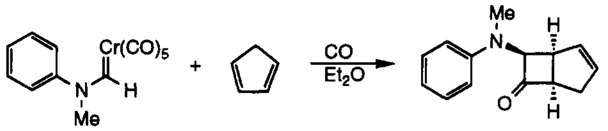
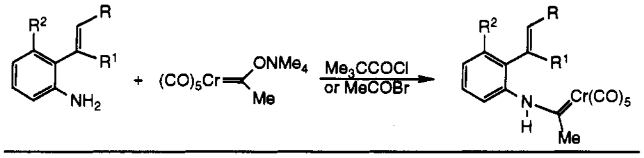


Table I. Synthesis of Fischer Amino Carbene Complexes



R	R^1	R^2	product (yield, %)
H	H	CO$_2$Me	**1a** (65)
Me	H	H	**1b** (70)
H	Me	H	**1c** (61)
H	H	H	**1d** (43)

In an attempt to achieve formation of cyclobutanones in an intramolecular fashion employing this protocol, the chromium complex **1a** having a vinyl substituent on the benzene ring was photolyzed. However, upon irradiation of a diethyl ether solution of the carbene complex **1a** under 3 atm of carbon monoxide using a medium-pressure Conrad-Hanovia mercury lamp, none of the expected fused cyclobutanone 4 was produced. 4-Carbomethoxy-2-methylindole (**2a**)[11] together with a small amount of a compound tentatively assigned as the fused indoline cyclopropane **3**[12] were isolated as sole products (Scheme II). The chemical yield from this reaction was low (26% and 10% yield, respectively, for **2a** and **3**). Although the yield of indole obtained from the photolytic reaction was fair at best, the reaction is interesting both from synthetic and mechanistic points of view. It was perceived that performing the reaction under thermal conditions may result in a higher yield of product. Thermal conditions are known to promote a number of inter- and intramolecular cyclization reactions of Fischer carbenes.[3–6] Thus, upon heating a toluene solution of **1a** to 120 °C for 20 h, a gratifying 60% yield of pure indole **2a** was isolated after chromatography.[13] Not only was the yield of product substantially improved but also no trace of the cylopropane **3** was seen by ^{1}H NMR of the crude reaction mixture. In addition to the indole **2a**, toluene complexed to chromium tricarbonyl was also isolated in 27% yield.

A plausible mechanism for the formation of **2a** and **3** is depicted in Scheme III. Loss of one of the chromium-

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[●] Abstract published in *Advance ACS Abstracts*, September 15, 1993.

(1) Presented in part by B.C.S. at the 17th NSF National Organometallic Chemistry Workshop, New Orleans, LA, May 13–16, 1993, and at the 33rd National Organic Chemistry Symposium, Bozeman, MT, June 13–17, 1993.

(2) Hegedus, L. S.; Bates, R. W.; Söderberg, B. C. *J. Am. Chem. Soc.* **1991**, *113*, 924 and references cited therein.

(3) Hegedus, L. S.; Imwinkelried, R.; Alarid-Sargent, M.; Dvorak, D.; Satoh, Y. *J. Am. Chem. Soc.* **1990**, *112*, 1109.

(4) For excellent reviews, see: (a) Chan, K. S.; Peterson, G. A.; Brandvold, T. A.; Faron, K. L.; Challener, C. A.; Hyldahl, C.; Wulff, W. D. *J. Organomet. Chem.* **1987**, *334*, 9. (b) Dötz, K. H. *Angew. Chem., Int. Ed. Engl.* **1984**, *27*, 587.

(5) For recent examples of intramolecular reactions, see: Söderberg, B. C.; Hegedus, L. S. *Organometallics* **1990**, *9*, 3113 and references cited therein. For recent examples of intermolecular reactions, see: (a) Harvey, D. F.; Brown, M. F. *J. Org. Chem.* **1992**, *57*, 5559. (b) Harvey, D. F.; Lund, K. P.; Neil, D. A. *J. Am. Chem. Soc.* **1992**, *114*, 8424.

(6) (a) Harvey, D. F.; Brown, M. F. *J. Org. Chem.* **1992**, *57*, 5559. (b) Harvey, D. F.; Lund, K. P.; Neil, D. A. *J. Am. Chem. Soc.* **1992**, *114*, 8424.

(7) Tumer, S. U.; Herndon, J. W.; McMullen, L. A. *J. Am. Chem. Soc.* **1992**, *114*, 8394.

(8) Merlic, C. A.; Burns, E. E.; Xu, D.; Chen, S. Y. *J. Am. Chem. Soc.* **1992**, *114*, 8722.

(9) Mori, M.; Watanuki, S. *J. Chem. Soc., Chem. Commun.* **1992**, 1082.

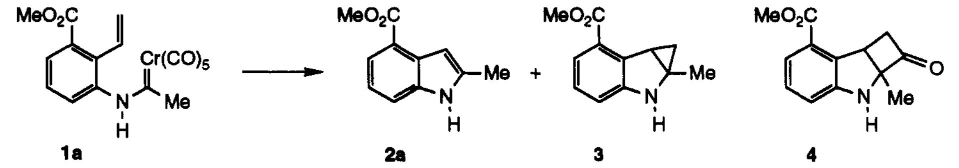
(10) Söderberg, B. C.; Hegedus, L. S. *J. Org. Chem.* **1990**, *56*, 2209.

(11) Spectral data (mp, IR, and ^{1}H NMR) were in complete accordance with literature values: Horning, D. E.; Lacasse, G.; Muchowski, J. M. *Can. J. Chem.* **1971**, *49*, 2797. Additional spectral data for **2a**: ^{13}C NMR (CDCl$_3$, 22.5 MHz) δ 168.4 (s), 137.8 (s), 136.9 (s), 128.7 (s), 124.3 (d), 120.1 (s), 119.9 (d), 115.0 (d), 101.7 (d), 51.6 (q), 13.7 (q).

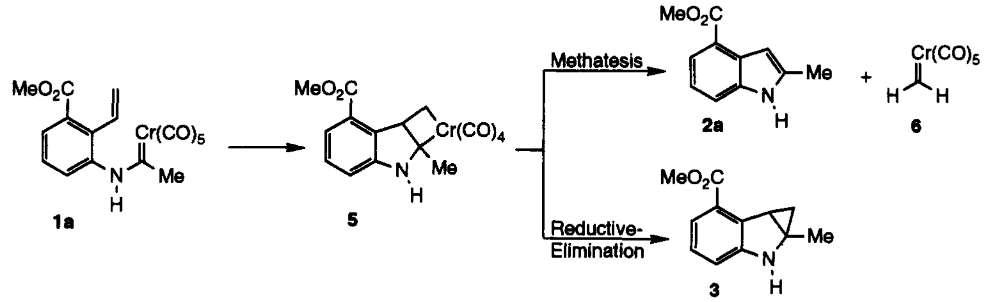
(12) The product changed overnight from a clear colorless oil into a yellow unidentified solid: ^{1}H NMR (CDCl$_3$, 90 MHz) of the oil δ 8.24 (d, J = 8.1 Hz, 1 H), 7.65 (dd, J = 7.8 and 1.0 Hz, 1 H), 7.26 (t, J = 7.8 Hz, 1 H), 4.0 (br s, 1 H), 3.93 (s, 3 H), 3.07 (dd, J = 9.3 and 4.7 Hz, CHCH_aH$_b$, 1H), 2.42 (s, 3 H), 1.41 (dd, J = 9.3 and 5.4 Hz, CHCH$_a$H$_b$ 1 H), 0.82 (t, J = 5.1 Hz, CHCH$_a$$H_b$, 1 H). For related chemical shifts and coupling constants of 2-oxa- and 2-azabicyclo[3.1.0]hexane systems, see: Söderberg, B. C.; Hegedus, L. S. *Organometallics* **1990**, *9*, 3113.

(13) A typical procedure for all thermal reactions discussed herein: An airless flask, equipped with a condenser, containing a 0.1 M toluene solution of the carbene was heated at 120 °C, under a nitrogen atmosphere, for 20–24 h. The resulting brown reaction mixture was cooled to ambient temperature and filtered through a 0.5-cm Celite pad. The pad was washed with toluene, and the solvent was removed from the filtrate under reduced pressure on a rotary evaporator to give a brown oil. The crude product was chromatographed on silica gel affording pure product.

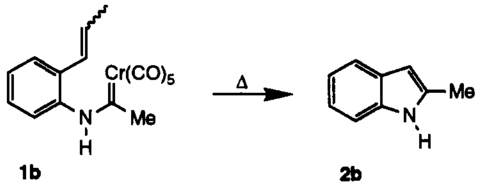
Scheme II



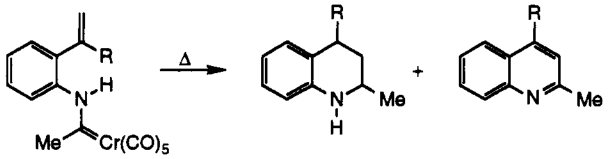
Scheme III



Scheme IV

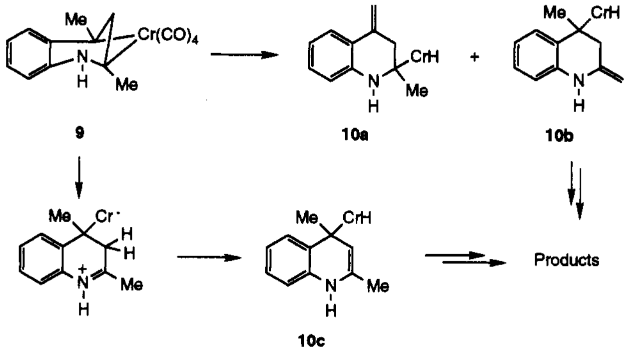


Scheme V



1c (R = Me, 0.1M)	7a (22%)	8a (34%)
1c (R = Me, 0.02M)		8a (53%)
1d (R = H, 0.1M)	7b (12%)	7b (21%)

Scheme VI



bound carbonyl ligands from the carbene complex enables the pendant double bond to coordinate with the metal followed by formation of the metallacyclobutane **5**. The metallacyclobutane then undergoes either metathesis to give **2a** or reductive elimination to give **3**. The highly unstable and very reactive pentacarbonyl(methylidene)-chromium (**6**), the second "half" from the metathesis reaction, has not been isolated and is presently only tentatively proposed as a product.[14]

A brief examination of the generality of the thermal reaction was undertaken, and a few novel arylamino-substituted carbene complexes, in addition to **1a**, were synthesized according to standard procedure.[15] Thus, tetramethylammonium pentacarbonyl(1-oxyethylidene)-chromium(0) was acylated, in dichloromethane at −40 °C, with trimethylacetyl chloride or acetyl bromide. The thermally labile acyloxy-substituted intermediates were treated with 2-(1-alkenyl)-substituted benzeneamines to afford, after column chromatography, the carbenes **1a–d** in fair to good yield (Table I). The isolated amino carbenes were found to be thermally unstable, even as neat compounds, and completely decompose when left overnight at ambient temperature. In most cases, ^{1}H NMR of the carbenes showed broad unresolved peaks due to rapid decomposition in solution.[16]

2-Methylindole **2b**[17] was obtained in 62% yield upon thermolysis of the carbene **1b**[18] in toluene, at 120 °C (Scheme IV). It should be noted that, except for **2a** and **2b**, no other organic products were observed by ^{1}H NMR of the crude reaction mixture for either of the two thermal reactions discussed.[19]

In contrast to the chromium carbenes complexes **1a** and **1b**, heating of a 0.1 M solution of complex **1c** in toluene

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(14) For some recent related metathesis reactions, see: (a) reference 9. (b) Hoye, T. R.; Suriano, J. A. *Organometallics* **1992**, *11*, 2044. (c) Harvey, D. F.; Lund, K. P. *J. Am. Chem. Soc.* **1991**, *113*, 5066. (d) Reference 10.

(15) A typical procedure for the preparation of all carbenes discussed herein: To a −40 °C solution of tetramethylammonium pentacarbonyl-(1-oxyethylidene)chromium(0) in CH_2Cl_2 (0.15 M), under a nitrogen atmosphere, was added 1 equiv of trimethylacetyl chloride or acetyl bromide via syringe. The resulting dark red solution was allowed to stir for 20 min keeping the temperature below −30 °C. The solution was recooled to −40 °C followed by addition of 1 equiv of benzeneamine dissolved in 10 mL of CH_2Cl_2. Upon slow warming to −20 °C the solution turned yellow. The reaction mixture was stored in a freezer at −20 °C overnight followed by stirring at ambient temperature for 1 h. Two teaspoons of silica gel was added, and the solvent was removed under reduced pressure on a rotary evaporator to give a yellow-orange solid residue. The crude product was chromatographed on silica gel eluting with CH_2Cl_2–hexanes (1:1) to afford the product as a yellow oil. The oil solidifies when stored at −20 °C. This procedure is a modification of: Hegedus, L. S.; Schwindt, M. A.; De Lombaert, S.; Imwinkelreid, R. *J. Am. Chem. Soc.* **1990**, *112*, 2264.

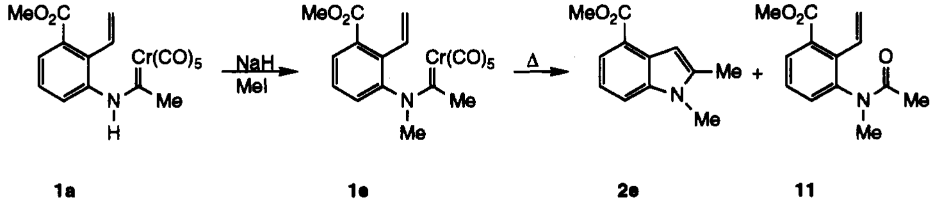
(16) The carbene **1b** was particularly unstable and we were unable to record a ^{13}C spectra. In addition, due to the thermal instability of **1a–e**, elemental analysis could not be performed.

(17) Spectral data (mp, ^{1}H NMR, IR) were in complete accordance with those of commercially available samples (Aldrich Chemical Co.).

(18) Compound **1b** was obtained as a 1:1 mixture of double bond isomers.

(19) A substantial amount of chromium hexacarbonyl can be recovered from the reflux condenser at the end of the reaction.

Scheme VII



did not produce an indole but gave an easily separable mixture of 2,4-dimethyl-1,2,3,4-tetrahydroquinoline (**7a**)[20] and 2,4-dimethylquinoline (**8a**)[17] (Scheme V). The tetrahydroisoquinoline **7a** was obtained as a 4.4:1 mixture (^{1}H NMR) of inseparable *cis–trans* isomers. In a separate experiment, 2,4-dimethylquinoline was the only product isolated when a lower concentration (0.02 M) of carbene was used. Related quinoline products, **7b** (*cis–trans* (1:1))[21] and **8b**,[17] were obtained from thermal reaction of **1d** (Scheme V). Only minor amounts of 2-methylindole (<5%) were isolated from the crude reaction mixture in the latter case. The reason for the selective formation of indoles in some cases and quinolines in others is presently not clearly understood.

A couple of mechanistic formalism can be entertained for the formation of the quinolines. A "twisted" [2 + 2] addition to form a bridged metallacyclobutane **9**, as exemplified for **1c**, is a logical first step in both mechanisms (Scheme VI). Similar results, with addition both in a straight and a twisted fashion, have been obtained in some cases from intramolecular [2 + 2] addition reactions between ketenes and alkenes forming cyclobutanones.[22,23] The metallacyclobutane **9** can then either undergo β-elimination in two different directions to form the σ-complexes **10a** and **10b**[24] or undergo an ionic cleavage followed by a proton shift to give **10c**.[25] A related mechanism, for the former route, including a twisted mode of cycloaddition followed by β-elimination, has been suggested in the intramolecular formation of 3,4-dihydropyranes from Fischer carbenes having a tethered alkene.[5] At this point, a few different possibilities for further reaction of **10a–10c** is apparent such as reductive elimination or a second β-elimination. The products from these eliminations are either compounds isomeric to the quinoline product and/or dihydroquinolines. The latter readily undergo disproportionation reactions to form quinolines and tetrahydroquinolines. A similar reduction of double bonds in the presence of chromium complexes has been reported.[26]

As a final carbene examined, the *N*-methyl-substituted complex **1e** was prepared in 89% yield by deprotonation of **1a** with sodium hydride followed by alkylation with iodomethane (Scheme VII). Thermolysis of **1e**, under similar reaction conditions as described above, gave a mixture of the indole **2e** and the amide **11** in a 21% and 30% yield, respectively. The amide is most likely formed by air oxidation of the chromium carbon double bond of the thermally and oxidatively labile carbene **1e**.

In summary, depending on the substitution pattern of the starting material, substituted indoles or quinolines are formed from arylamino-substituted Fischer chromium carbenes having a 1-alkenyl substituent in the ortho position of the benzene ring. We are currently investigating the scope and limitation of these novel reactions.

Acknowledgment. This research was generously supported by grants from the National Science Foundation (CHE-9203146) and, in part, from the University of South Alabama Research Council.

Supplementary Material Available: Spectral data for compounds **1a–e**, **2e**, and **11** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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[20] Spectral data for **7a** (IR and ^{1}H NMR): Hegedus, L. S.; Allen, G. F.; Bozell, J. J.; Waterman, E. L. *J. Am. Chem. Soc.* **1978**, *100*, 5800 and references cited therein. Additional spectral data for **7b**: ^{13}C NMR (CDCl$_3$, 22.5 MHz) δ 129.2, 126.7, 120.8, 118.9, 117.2, 114.1, 47.2, 30.0, 26.5, 22.5.

[21] Spectral data for **7b** (IR, MS, and ^{1}H NMR) were in complete accordance with literature values: Shaw, J. E.; Stapp, P. R. *J. Heterocycl. Chem.* **1987**, *24*, 1477.

[22] For an excellent review on intramolecular ketene–alkene cycloadditions, see: Snider, B. B. *Chem. Rev.* **1988**, *88*, 793.

[23] Söderberg, B. C.; Hegedus, L. S.; Sierra, M. A. *J. Am. Chem. Soc.* **1990**, *112*, 4364.

[24] In the case of **1d**, the only available protons in a cis-relationship to the metal required for the β-elimination are situated on the methyl group α to the nitrogen atom; thus, only one elimination intermediate is possible.

[25] This mechanism was suggested by one of the reviewers.

[26] Tumer, S. U.; Herndon, J. W.; McMullen, L. A. *J. Am. Chem. Soc.* **1992**, *114*, 8394 and references cited therein.