ORGANIC LETTERS

1999
Vol. 1, No. 1
161−164

Novel [1,5] Sigmatropic Rearrangements of Cyclohexadienones Generated from Fischer Carbene Complexes. A New Strategy for Installing the C-20 Angular Ethyl Group in Aspidospermidine Alkaloids

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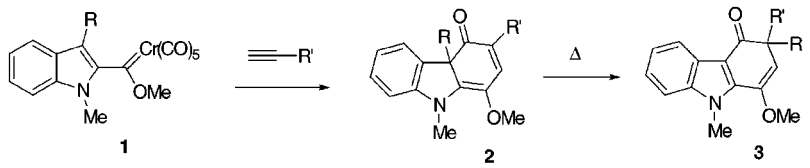
Received April 29, 1999

ABSTRACT



We report here the first examples of a [1,5] sigmatropic rearrangement in a 4a-alkyl-4a-hydrocarbazol-4-one to yield a 3-alkylcarbazol-4-one with a re-aromatized indole nucleus. The reaction of 1-methyl-3-substituted-indole-2-carbene complexes 1 with terminal alkynes yields 3,4a-dialkyl-1-methoxy-9-methylcarbazol-4-ones 2. These 4a-substituted carbazolones thermally rearrange to cleanly give the more highly aromatic 3,3-dialkyl-1-methoxy-9-methylcarbazol-4-ones 3. This reaction provides a convenient entry to the Aspidosperma family of alkaloids, which contain a 3,3-disubstituted carbazole nucleus.

In the course of investigating the synthetic applications of Fischer carbene complex chemistry to indole alkaloid synthesis, we have recently discovered a novel [1,5] sigmatropic rearrangement.[1] Sigmatropic rearrangements have proven to be extremely powerful tools for the construction of complex carbon frameworks.[2] Anion accelerated [3,3] processes such as the oxy-Cope and Claisen rearrangements have received the most attention,[3] while [1,5] shifts other than hydrogen are relatively unknown.[4]

Our approach[5] to the synthesis of the pentacyclic Aspidosperma indole alkaloid, vindoline **7**,[6] involves the cyclohexadienone annulation[7] of the 1,3-disubstituted-indol-2-yl carbene complex **5** with alkyne **4** to yield the 4a-substituted carbazol-4-one **6**. These compounds were anticipated to furnish the required pentacyclic skeleton via a double intramolecular reductive amination (Scheme 1).

Initial investigations to demonstrate the feasibility of this strategy centered around the simplified 1,3-dimethylindole carbene complex **8**. We previously reported that this complex would react with a number of alkynes to give the desired cyclohexadienones in good yields as is illustrated by its reactions with 1-pentyne and 3-hexyne in Scheme 2, which gave the 4a-carbazolones **9a** and **9b** in 85 and 95% yields, respectively.[8]

(1) For reviews on [1,5] thermal sigmatropic rearrangements, see: (a) Spangler, C. W. *Chem. Rev.* **1976**, *76*, 187. (b) Mironov, V. A.; Fedorovich, A. D.; Akhrem, A. A. *Russ. Chem. Rev.*, **1981**, *50*, 666.

(2) For a review on the Cope and Claisen rearrangements, see: Rhoads, S. J.; Raulins, N. R. *Org. React.* **1975**, *22*, 1.

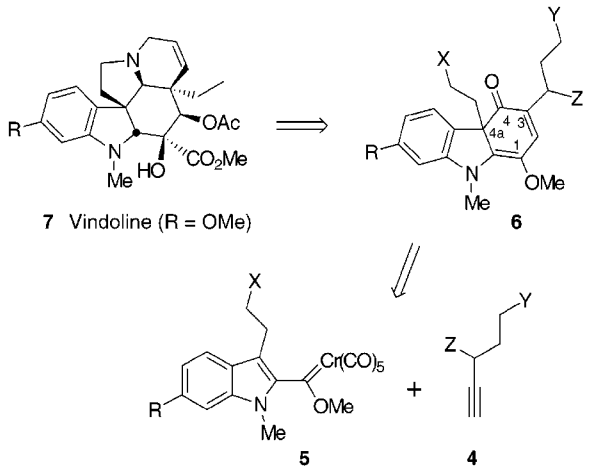
(3) For reviews, see: (a) Wilson, S. R. *Org. React.* **1993**, *43*, 93. (b) Bronson, J. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Flemming, I., Eds.; Pergamon Press: 1991; Vol. 5, p 999.

(4) For examples of anion-accelerated [1,5] alkyl shifts, see: Battye, P. J.; Jones, D. W. *J. Chem. Soc., Chem. Commun.* **1984**, 990.

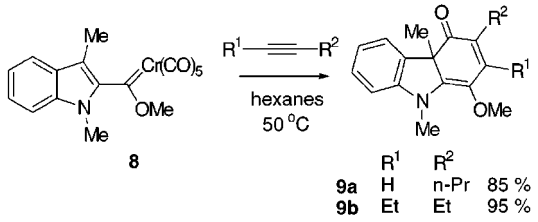
(5) Bauta, W. E.; Wulff, W. D.; Pavkovic, S. F.; Zaluzec, E. J. *J. Org. Chem.* **1989**, *54*, 3249.

10.1021/ol990063q CCC: $18.00
Published on Web 05/26/1999

Scheme 1

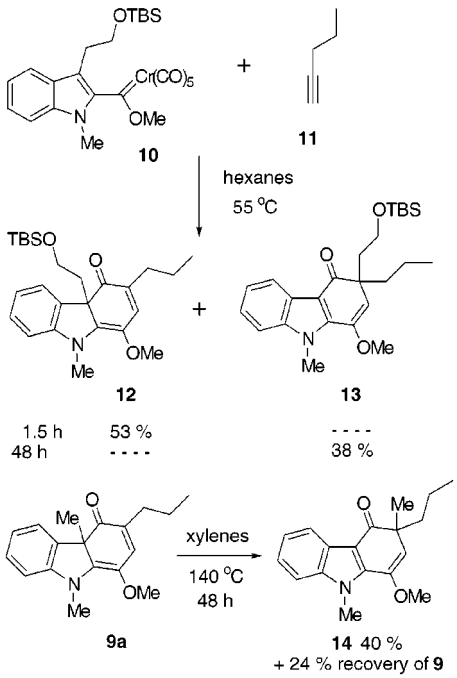


Scheme 2



Upon cyclohexadienone annulation of 1-pentyne with the more highly functionalized carbene complex **10** derived from a silyl-protected tryptophol,[9] it was found that, in addition to the desired cyclohexadienone product **12**, the product resulting from a [1,5] sigmatropic rearrangement of **12** was also present (Scheme 3). If the reaction is carried out at 55 °C for 90 min, only the cyclohexadienone **12** was observed and the same reaction for 48 h provided only the rearranged cyclohexadienone **13**. Initially, this result seemed surprising

Scheme 3



since the rearranged product **14** has never been seen in the reaction of **10**. However, it was found that **9a** could be partially rearranged to **14** by refluxing in xylenes for 48 h.

The formation of cyclohexadienones from the reaction of aryl carbene complexes in which both ortho positions are substituted up until now has been limited to indole carbene complexes.[10] It has been previously reported that the reaction of the 2,6-dimethylphenyl complex **15** in butyl ether with diphenylacetylene gave the indenes **16** and **17** in a total yield of 52%.[11] We have reinvestigated the reaction of complex **15** with a number of different alkynes, and the results are presented in Scheme 4. The reaction gives excellent yields with a number of internal alkynes in benzene, but reactions with terminal alkynes only give small quantities of characterizable materials and this may be due to the multiple insertion of the alkyne to give oligiomers. The formation of the indene **16e** in 84% yield as a 13:1 mixture of regioisomers demonstrates that silylated alkynes can be used as synthons for terminal alkynes. While we did not detect any CO insertion products from the intermolecular reaction of complex **15** with alkynes, we did find that the intramolecular reaction of complex **18** gave a 37% yield of the cyclohexadienone **20** and a 17% yield of the indanone **19** resulting from the hydrolysis of an indene product. This is the first example of the formation of a cyclohexadienone from a 2,6-disubstituted-phenyl carbene complex.[12]

(6) For reviews, see: (a) Saxton, J. E. *Nat. Prod. Rep*. **1987**, *4*, 591. (b) Overman, L. E.; Sworin, M. In *Alkaloids, Chemical and Biological Perspectives*, Vol. 3; Pelletier, S. W., Ed.; Wiley: New York, 1985; p 275. (c) Cordell, G. A. In *The Alkaloids*; Manske, R. H. F., Rodrigo, R. G. A., Eds.; Academic Press: New York, 1979; Vol. XVII, p 199. For citations, see: (d) Magnus, P.; Gallagher, T.; Brown, P.; Pappalardo, P., *Acc. Chem. Res*. **1984**, *17*, 35. For recent citations, see: (e) Feldman, P. L.; Rapoport, H. *J. Am. Chem. Soc*. **1987**, *109*, 1603. (f) Node, M.; Nagasawa, H.; Fuji, K. *J. Am. Chem. Soc*. **1987**, *109*, 7901. (g) Kuehne, M. E.; Zebovitz, T. C. *J. Org. Chem*. **1987**, *52*, 4331. (h) Brennan, J. P.; Saxton, J. E. *Tetrahedron* **1987**, *43*, 191. (i) Cardwell, K.; Hewitt, B.; Ladlow, M.; Magnus, P. *J. Am. Chem. Soc*. **1988**, *110*, 2242. (j) Hugel, G.; Pfeuffer, L. *Tetrahedron Lett*. **1987**, *28*, 1773. (k) Ogawa, M.; Kitagawa, Y.; Natsuma, M. *Tetrahedron Lett*. **1987**, *28*, 3985. (l) Jackson, A. H.; Shannon, P. V. R.; Wilkens, D. J. *Tetrahedron Lett*. **1987**, *28*, 4901.

(7) (a) Tang, P. C.; Wulff, W. D. *J. Am. Chem. Soc*. **1984**, *106*, 1132. (b) Wulff, W. D.; Yang, D. C. *J. Am. Chem. Soc*. **1984**, *106*, 7565. (c) Wulff, W. D.; Gilbertson, S. R. *J. Am. Chem. Soc*. **1985**, *107*, 503. (d) Wulff, W. D.; Kaesler, R. W.; Peterson, G. A.; Tang, P. C. *J. Am. Chem. Soc*. **1985**, *107*, 1060. (e) Semmelhack, M. F.; Park, J. *Organometallics* **1986**, *5*, 2550.

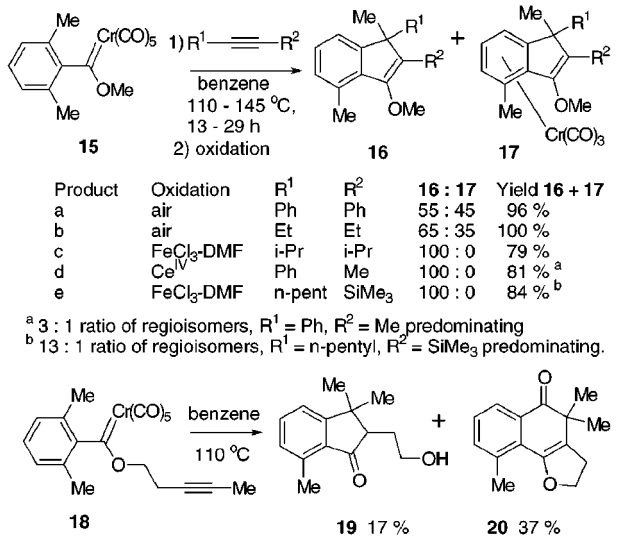
(8) Bauta, W. E.; Wulff, W. D.; Pavkovic, S. F.; Zaluzec, E. J. *J. Org. Chem*. **1989**, *54*, 3249.

(9) The carbene complex **10** was prepared in 67% yield from *N*-methyl-*O*-*tert*-butyldimethylsilyltryptophol by the method shown for complex **37** in Scheme 7.

(10) (a) Dötz, K. H.; Dietz, R.; Appenstein, C. K.; Neugebauer, D.; Schubert, U. *Chem. Ber*. **1979**, *112*, 3682. (b) Dötz, K. H.; Sturm, W. *J. Organomet. Chem*. **1986**, *310*, C22. (c) Bos, M. E.; Wulff, W. D.; Wilson, K. J. *J. Chem. Soc., Chem. Commun*. **1996**, 1863. (d) Harrity, J. P. A.; Kerr, W. J.; Middlemiss, D.; Scott, J. S. *J. Organomet. Chem*. **1997**, *532*, 219.

(11) Dötz, K. H.: Dietz, R.; Appenstein, C. K.; Neugebauer, D.; Schubert, U. *Chem. Ber*. **1979**, *112*, 3682.

Scheme 4

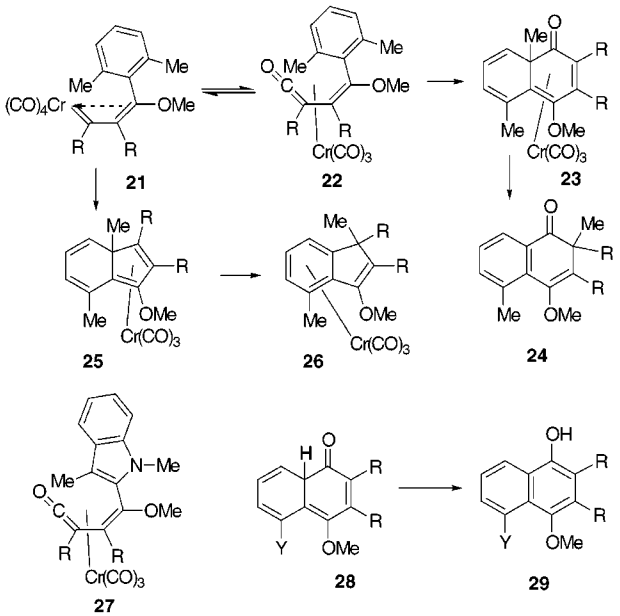


Product	Oxidation	R^1	R^2	16 : 17	Yield 16 + 17
a	air	Ph	Ph	55 : 45	96 %
b	air	Et	Et	65 : 35	100 %
c	$FeCl_3$-DMF	i-Pr	i-Pr	100 : 0	79 %
d	Ce^{IV}	Ph	Me	100 : 0	81 % [a]
e	$FeCl_3$-DMF	n-pent	$SiMe_3$	100 : 0	84 % [b]

[a] 3 : 1 ratio of regioisomers, R^1 = Ph, R^2 = Me predominating
[b] 13 : 1 ratio of regioisomers, R^1 = n-pentyl, R^2 = $SiMe_3$ predominating.

The normal course of events in the reaction of alkynes with aryl Fischer carbene complexes containing at least one ortho hydrogen substituent is initial loss of a carbon monoxide ligand, insertion of an alkyne to generate a vinyl carbene complexed intermediate of the type **21**, insertion of a CO ligand to give a vinyl ketene complex of the type **22**, electrocyclic ring closure to give a cyclohexadienone intermediate of the type **28**, and then finally tautomerization to the naphthol **29** which is the ultimate product of the reaction (Scheme 5).[13] Two differences that are seen in the intermolecular annulations of 2,6-disubstituted phenyl complexes are that CO-inserted products are not seen and that the temperatures required are 50−60 °C higher under otherwise similar conditions. The higher temperature requirement suggests that the initial dissociation of a CO ligand is no longer the rate-limiting step of the reaction. It is possible that the electrocyclic ring closure of the vinyl ketene intermediate is now the slow step in the sequence, and this would explain the results described above.

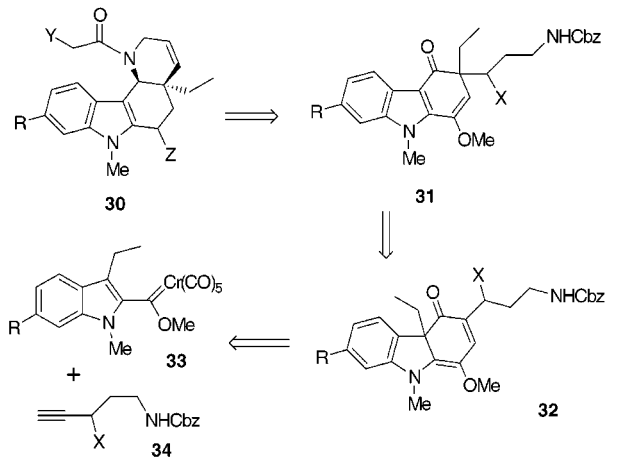
Scheme 5



The reason that the intramolecular reaction of complex **18** gives cyclohexadienone **20** may be related to a conformation restriction in the vinyl ketene that is favorable to the transition state for ring closure. In no reactions were the isoindene **25** or the isomeric cyclohexadienone **23** isolated. These intermediates undergo [1,5] sigmatropic migration of methyl faster than the corresponding indole intermediate **9a**, which can be isolated and which only undergoes rearrangement slowly at 140 °C. This is presumably due to the fact that there is a greater driving force in the restoration of aromaticity in the phenyl systems compared to the indole intermediates.[14] Assuming that the methyl groups in **21** do not slow the rate of CO insertion, the isolation of indenes as the only product in the intermolecular reaction would require that CO insertion was reversible. While there is no experimental or theroetical evidence for this, it is not unreasonable in these ortho-disubstituted complexes. What is not so clear is why the cyclization to the isoindene **25** would be more favorable than that to the cyclohexadienone **23**. Perhaps the [1,5] sigmatropic shift is rate-limiting in each case and is faster in **25** than in **23** due to better orbital overlap.

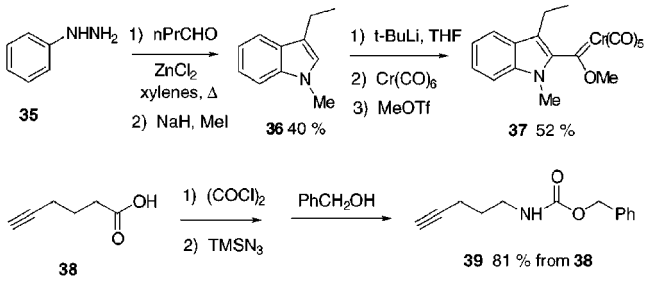
The [1,5] sigmatropic shifts of alkyl substituents observed for the carbazolones **12** and **9a** prompted the consideration of a new strategy for the synthesis of members of the Aspidospermidine alkaloid family which is outlined in Scheme 6. It begins with a cyclohexadienone annulation of a 3-ethyl-2-indolyl carbene complex like **33** with an N-protected 1-amino-4-pentyne like **34**. The thermal rearrangement of the carbazolone **32** will relocate the ethyl group to the nascent C-20 position of the aspidospermidine ring system. After installation of the piperidine ring to produce the tetracycle **30**, all that would remain is to append the pyrrolidine ring to complete the construction of the pentacyclic Aspidosperma carbon skeleton.[15]

Scheme 6



As a test of this strategy, the 3-ethyl-2-indolyl Fischer carbene complex **37** and the alkyne **39** were prepared as outlined in Scheme 7. The requisite 3-ethylindole was

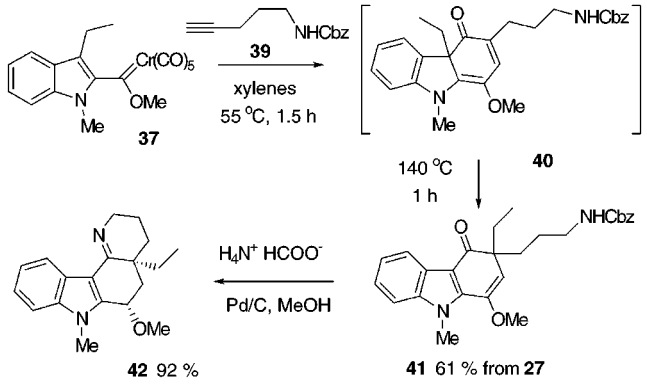
Scheme 7



prepared by a Fischer indole synthesis from phenylhydrazine and *n*-butyraldehyde.[16] The carbene complex **37** was prepared from indole **36** by the standard Fischer procedure involving the reaction of chromium carbonyl with the 2-indolyllithium which was generated by metalation with *tert*-butyllithium.[17] The preparation of the protected 1-amino-4-pentyne **39** was accomplished in one pot in 81% yield by a Curtius rearrangement of the commercially available acid **38** by the procedure of Nägeli where trimethylsilyl azide is substituted for sodium azide followed by trapping the isocyanate with benzyl alcohol.[18]

The cyclohexadienone annulation of complex **37** and alkyne **39** was carried out in xylenes at 55 °C for 90 min followed by heating at 140 °C to effect the [1,5] sigmatropic shift of the ethyl group which was complete after 1 h to give the 3,3-disubstituted carbazolone **41** in 61% overall yield (Scheme 8). From the point of view of this new strategy for

Scheme 8



the synthesis of Aspidospermidine alkaloids, it is important to note that the [1,5] sigmatropic shift of the ethyl group in **37** was much faster than that for the methyl group in **9a** (Scheme 3). The carbazolone **41** was additionally characterized by treatment with ammonium formate in the presence of palladium on carbon which resulted in deprotection of the amine, cyclization to the imine, and reduction of the enol ether to give a single diastereomer of the methyl ether **42** in 92% yield.

The successful transformation of indole **36** to the carbazolone **41** demonstrates the feasibility of a new strategy for the synthesis of Aspidospermidine alkaloids involving a [1,5] sigmatropic shift of an ethyl group from a 3,4a-disubstituted carbazolone. Further studies to evaluate the overall efficiency of this strategy will be reported in due course

Acknowledgment. This work was supported by a grant from the National Institutes of Health.

Supporting Information Available: Experimental procedures and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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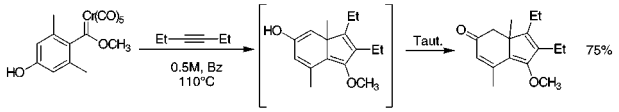
(12) An exception is when the rearomatization is thwarted by a tautomerization: Bos, M. E.; Wulff, W. D.; Wilson, K. J. *J. Chem. Soc., Chem. Commun.* **1996**, 1863.

(13) (a) Hofmann, P.; Hämmerle, M.; Unfried, G. *New. J. Chem.* **1991**, *15*, 769. (b) Hofmann, P.; Hämmerle, M. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 908. (b) Gleichmann, M. M.; Dötz, K. H.; Hess, B. A., *J. Am. Chem. Soc.* **1996**, *118*, 10551. (c) Torrent, M.; Duran, M.; Sola, M. *J. Chem. Soc., Chem. Commun.* **1998**, 999. (d) Bos, M. E.; Wulff, W. D.; Miller, R. A.; Chamberlin, S.; Brandvold, T. A. *J. Am. Chem. Soc.* **1991**, *113*, 9293.

(14) In the case of 2,6-disubstituted-4-hydroxyphenyl carbene complexes, the intermediate tautomerizes faster than it rearranges. Boss, M. E.; Wulff, W. D.; Wilson, K. J. *J. Chem. Soc., Chem. Commun.* **1996**. 1863.



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