Synthesis of Substituted Pyrroles via Zirconocene Complexes of Imines[†]

Stephen L. Buchwald,*[,1a] M. Woods Wannamaker,[1b] and Brett T. Watson[1c]

Department of Chemistry
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

Received September 2, 1988

The use of transition metals in organic synthesis has increased tremendously in recent years.[2] The success of transition-metal-based organic synthesis is due in part to the unique ability of the metal to activate ligands to which it is directly bound. Moreover, organometallic transformations are often highly chemo-, regio-, and stereoselective processes. Recent efforts have realized the development of expedient routes to highly functionalized carbocyclic systems.[3] However, with the exception of β-lactams, transition-metal-based routes to nitrogen-containing heterocycles have been explored to a lesser extent.[4] We have recently reported on the preparation and study of a variety of imine complexes of zirconocene **4**.[5] These complexes, which can be generated and allowed to react without isolation, regioselectively insert alkynes to give azametallacyclopentenes **5** (Scheme I). As a part of a program concerned with the development of new methods for organic synthesis involving organozirconocene complexes,[6] we became interested in the possibility of replacing the zirconocene group in **5** with carbon monoxide (CO) as a possible route to nitrogen-containing heterocycles. In this communication we report a new synthesis of substituted pyrroles formed by reaction of the metallacycles **5** with carbon monoxide.

We initially anticipated that carbonylation of metallacycles **5** would produce the pyrrolinones **7**. However, we were surprised to find that the reaction of **5** with CO takes an entirely different course to afford substituted pyrroles **6**. Thus, when **5a** (R = C_6H_5, R^1 = H, R^2 = $CH_2CH_2CH_3$), which can be prepared and transferred to a Fischer-Porter bottle without isolation, was carbonylated [(CO, 90 psi), 80 °C, THF, 48 h] followed by aqueous workup and chromatography, a 56% yield of 2-phenyl-4-(*n*-propyl)pyrrole (**12**) was obtained.[7] No evidence of the corresponding pyrrolinone was observed. The formation of the pyrrole **12** during carbonylation of **5a** represents a significant deviation from traditional methods of pyrrole synthesis which usually utilize carbonyl precursors.[8,9] In contrast, the above method employs simple, readily available starting materials—unactivated alkynes, amines, and carbon monoxide. Moreover, since the reaction is performed under neutral conditions, problems associated with the presence of a reactive carbonyl functionality are circumvented.[8] It is significant that the metallacycles **5** can be prepared and converted to pyrroles without need of isolation

Scheme I

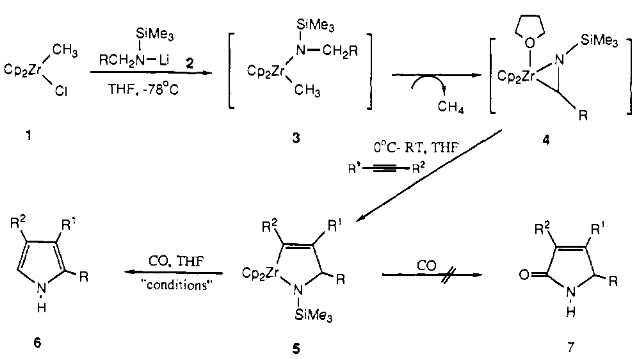
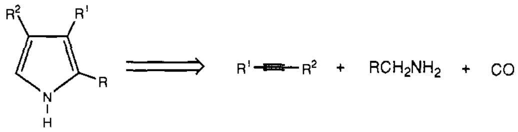
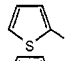
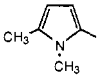
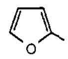


Table I.



entry	R	R^1	R^2	yield[a] (%)	conditions[b]
1	C_6H_5	H	C_6H_5	69	A
2	C_6H_5	H	H	41	C
3	C_6H_5	C_6H_5	C_6H_5	49	A
4	C_6H_5	CH_3	CH_3	44	C
5	C_6H_5	H	$CH_2CH_2CH_3$	56	A
6	C_6H_5	H	CH_2OTBS	31	A
7	C_6H_5	H	$SiMe_3$	15	B
8	C_6H_5	H	$CH_2CH_2CH_2CN$	48	A
9	H	CH_3	CH_3	24	A
10	H	$n$$C_8H_{17}$	H	40	A
11	$n$$C_5H_{11}$	C_6H_5	C_6H_5	54	A[c]
12	$n$$C_5H_{11}$	H	C_6H_5	53	A[c]
13		H	$CH_2CH_2CH_3$	41	C
14		H	$CH_2CH_2CH_3$	68	A
15		H	C_6H_5	49	A

[a] Yields are isolated yields based on 1 equiv of amine. [b] Method A: 5.0 mmol of **5**, 50 mL of THF, 3 equiv of NH_4Cl, 1500 psi CO, room temperature, 24 h; method B: identical with A except 500 mg of activated, degassed, 2-3 μm, 4 Å molecular sieves were used instead of NH_4Cl; method C: identical with A except the reaction is performed in a Fischer-Porter bottle at 80-90 psi CO at 80 °C *without* added NH_4Cl. [c] Carbonylated for 36 h using method A.

[†] Dedicated to Professor Satoru Masamune on the occasion of his 60th birthday.

(1) (a) Dreyfus Grantee for Newly Appointed Faculty in Chemistry, 1984-1989; American Cancer Society Junior Faculty Research Awardee 1987-1989; Eli Lilly Grantee 1988-1990; Alfred P. Sloan Research Fellow, 1988-1990; Union Carbide Innovation Recognition Program Awardee, 1988. (b) NIH Postdoctoral Fellow (GM-11529) 1986-1988. Present address: Merrell Dow Research Institute, Cincinnati, OH 45215. (c) Recipient of an American Chemical Society Organic Division Graduate Fellowship sponsored by the Dow Chemical Company.

(2) (a) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987. (b) Hegedus, L. S. *J. Organomet. Chem. Libr.* **1987**, (*Organomet. Chem. Rev.*; *Annu. Surv.*) *19*, 1-269. (c) Hegedus, L. S. *J. Organomet. Chem.* **1986**, *298*, 207-453. (d) Blagg, J.; Davies, S. G.; Gordon, P. F. *Gen. Syn. Methods*, **1987**, *9*, 398.

(3) *Tetrahedron Symposia in Print*; Semmelhack, M. F., Ed., **1985**, *42*, 5741-5887.

(4) For some representative examples cf: Reviews: (a) Hegedus, L. S. *Organic Synthesis: Interdisciplinary Challenge. Proceedings of the IUPAC Symposium*, 5th meeting, Streith, J., Prinzbach, H., Schill, G., Eds.; Blackwell: Oxford, UK, 1985; pp 17-24. (b) Ohshiro, Y.; Hirao, T. *Heterocycles* **1984**, *22*, 859. β-lactams: (c) Liebeskind, L. S.; Welker, M. E.; Fengel, R. F. *J. Am. Chem. Soc.* **1986**, *108*, 6328. (d) Davies, S. G.; Hedgecock, D.; Isabelle, M.; Sutton, K. H.; Walker, J. C.; Rones, R.; Prout, K. *Tetrahedron* **1986**, *42*, 5123. (e) Borel, C.; Hegedus, L. S.; Krebs, J.; Satoh, Y. *J. Am. Chem. Soc.* **1987**, *109*, 1101. (f) Hegedus, L. S.; Weck, G.; D'Andrea, S. *J. Am. Chem. Soc.* **1988**, *110*, 2122. (g) Hegedus, L. S.; D'Andrea, S. *J. Org. Chem.* **1988**, *53*, 3113. (h) Hodgson, S. T.; Hillinshead, D. M.; Ley, S. V. *Tetrahedron* **1985**, *42*, 5871. Pyridines: (i) Parnell, C. A.; Vollhardt, K. P. C. *Tetrahedron* **1985**, *41*, 5791. Indoles: (j) Harrington, P. J.; Hegedus, L. S.; McDaniel, K. F. *J. Am. Chem. Soc.* **1987**, *109*, 4335. Pyrroles: (k) Trost, B. M.; Keinan, E. *J. Org. Chem.* **1980**, *45*, 2743. (l) Utimoto, K.; Miw, H.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 4277. Other nitrogen containing heterocycles: (m) Chan, K. S.; Wulff, W. D. *J. Am. Chem. Soc.* **1986**, *108*, 5229. (n) Hegedus, L. S. *J. Mol. Catal.* **1983**, *19*, 201. (o) Hoberg, H.; Oster, B. W. *J. Organomet. Chem* **1983**, *252*, 359. (p) Mori, M.; Chiba, K.; Inotsume, N.; Ban, Y. *Heterocycles* **1979**, *12*, 921. (q) Alper, H.; Mahatantila, C.; Einstein, F.; Willis, A. *J. Am. Chem. Soc.* **1984**, *106*, 2708.

(5) Buchwald, S. L.; Watson, B. T.; Wannamaker, M. W.; Dewan, J. C., submitted for publication.

(6) Buchwald, S. L.; Watson, B. T.; Lum, R. T.; Nugent, W. A. *J. Am. Chem. Soc.* **1987**, *109*, 7137.

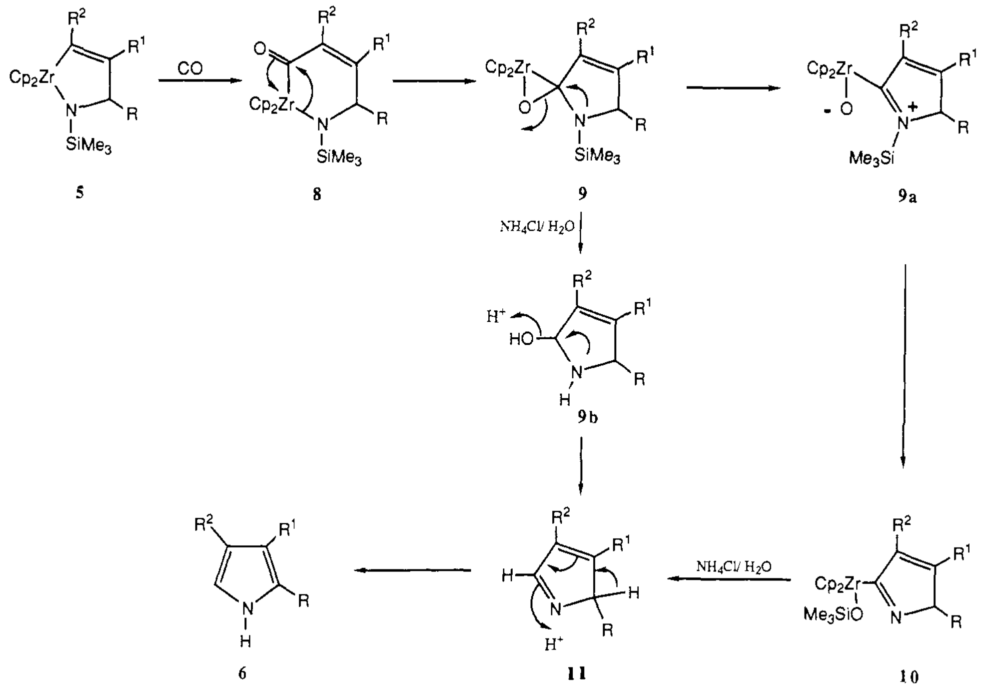
(7) All new compounds were characterized by ^1H NMR, ^{13}C NMR, IR, and high resolution mass spectrometry. Details are available in the Supplementary Material along with representative experimental procedures.

(8) (a) Jones, R. A.; Bean, G. P. *The Chemistry of Pyrroles*; Blomquist, A. T., Wasserman, H. H., Ed.; Academic Press: New York, 1977. (b) For a unique route to pyrroles cf.: Corriu, R. J. P.; Moreau, J. E.; Vernhet, C. *Tetrahedron Lett.* **1987**, *28*, 2963 and references therein.

(9) Katritzky, A. R.; Rees, C. W. *Comprehensive Heterocyclic Chemistry*; Bird, C. W., Cheeseman, G. W. H., Eds.; Pergamon Press: New York, 1984; Vol. 4.

0002-7863/89/1511-0776$01.50/0

Scheme II



since in this manner the entire reaction sequence can be performed in essentially a one flask operation from an amine starting material. This piecewise construction of pyrroles from smaller, readily available materials has the advantage that one can prepare a wide range of pyrroles using a single synthetic method.

In view of these considerations, we have studied this unique transformation in an effort to define its scope and synthetic utility. The results of our investigations are summarized in Table I. As can be seen, the reaction tolerates a variety of substituents affording di- and trisubstituted pyrroles. After some experimentation, we have found that the reaction is best performed in the presence of 3 equiv of solid ammonium chloride at a pressure of 1500 psi of carbon monoxide (method A) in THF at room temperature.[7] Under these conditions, the carbonylation is usually complete within 24 h. Although the role of the ammonium chloride is unclear, we have observed that in the absence of the ammonium chloride, the crude reaction mixture contains highly colored impurities which complicate purification. Yields[10] range from moderate to excellent and indicate the yield of isolated pyrrole, based on 1 equiv of starting amine with neither isolation nor purification of any intermediates. Lowered yields may be due in part to oxidation of these electron-rich alkyl and aryl pyrroles.[9]

Table I contains a number of examples which merit discussion. First, the reaction works for activated as well as unactivated amines. That the reaction sequence will tolerate a variety of functional groups is demonstrated by entries 6–8. Thus, it is possible to prepare pyrroles containing the siloxymethyl, trimethylsilyl, and 3-cyanopropyl substituents. The reaction is apparently sensitive to steric factors as is indicated by entry 7 (R^2 = $SiMe_3$). As illustrated by entry 2, it is also possible to obtain 2-substituted pyrroles when acetylene is used as the alkyne. Of particular interest are entries 13–15 which demonstrate that good yields of 2,2′-heterocyclic substituted pyrroles[11] can be achieved with this methodology. Compounds of this type are of interest both as intermediates in natural product synthesis[12] and in the preparation of new ligands for transition-metal complexes. We are currently working to extend this work to include the preparation of 2,3′- and 3,3′-bipyrroles.[13]

Our mechanistic rationale to account for the formation of pyrroles **6** is shown in Scheme II. Insertion of CO into the C–Zr[14] bond would produce the metallacycle **8**. That the acyl group in **8** would be η^2 is well precedented[14] and this should increase the electrophilicity of the acyl carbon. Migration of the nitrogen atom from zirconium to the acyl carbon (formally a reductive elimination) would produce the zirconocene complex **9**. Intermediate **9** may undergo a nitrogen-assisted ring opening[8b] to give the zwitterion **9a** which can abstract the silyl group to give **10**. Hydrolysis of **10** to **11** followed by prototropic rearrangement produces the pyrrole **6**. Alternatively, **9** may be hydrolyzed to the alcohol **9b** which can lose water to produce **11**. Subsequent rearrangement of **11** gives pyrrole **6**. It should be noted that we have as yet been unable to isolate or spectroscopically characterize any of the proposed intermediates **8**–**10**.

In summary, we have developed a convenient method for the formation of substituted pyrroles from a primary amine, an unactivated alkyne, and carbon monoxide. We believe that the experimental simplicity, the generality, and the mildness of the reaction conditions should allow the application of this methodology for the preparation of a wide range of useful substituted pyrroles. We are continuing to investigate the mechanistic details and the use of this reaction for the formation of more complex pyrrole systems and will report our findings in due course.

Acknowledgment. We would like to thank Dr. Alfred Bader, Eli Lilly, the American Cancer Society, the National Institutes of Health (GM-34917), and Firmenich SA for their financial support. M.W.W. gratefully acknowledges a postdoctoral fellowship from the NIH. B.T.W. gratefully acknowledges an American Chemical Society Organic Division Graduate Fellowship sponsored by the Dow Chemical Company.

Supplementary Material Available: Experimental Section with representative procedures along with spectroscopic data for all compounds reported (9 pages). Ordering information is given on any current masthead page.

---

[10] All yields refer to isolated yields of compounds of greater than 95% purity as determined by capillary GC and ^{1}H NMR.

[11] (a) Boger, D. L.; Patel, M. *Tetrahedron Lett.* **1987**, *28*, 2499. (b) Hinz, W. H.; Patel, S. U.; Karatza, M. H. *Tetrahedron* **1986**, *42*, 3753.

[12] Boger, D. L.; Coleman, R. S. *J. Am. Chem. Soc.* **1987**, *109*, 2717.

[13] (a) Magnus, P.; Gallagher, T.; Schultz, J.; Or, Y. S.; Ananthanarayan, T. P. *J. Am. Chem. Soc.* **1987**, *109*, 2706. (b) Carter, P.; Fitzjohn, S.; Halazy, S.; Magnus, P. *J. Am. Chem. Soc.* **1987**, *109*, 2711.

[14] (a) Fachinetti, G.; Floriani, C. *J. Organomet. Chem.* **1974**, *71*, C5. (b) Fachinetti, G.; Floriani, C.; Stoeckli-Evans, H. *J. Chem. Soc., Dalton Trans.* **1977**, 2297. (c) Fachinetti, G.; Floriani, C.; Marchetti, F.; Merlino, S. *J. Chem. Soc., Chem. Commun.* **1976**, 522.