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Synthesis of Pyrroles through Coupling of Enyne-hydrazones with Fischer Carbene Complexes

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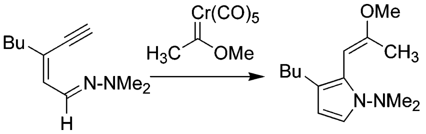
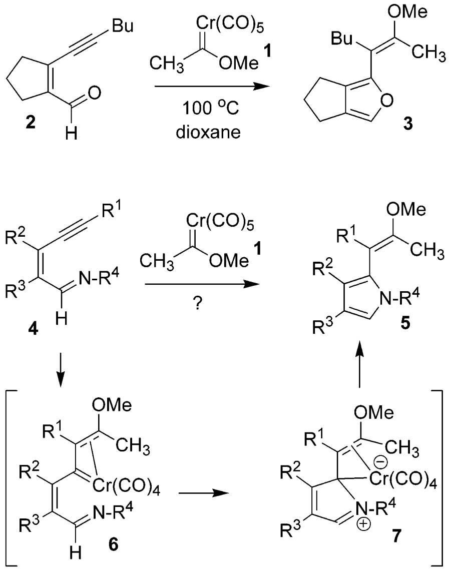
ABSTRACT



The coupling of enyne-imines with Fischer carbene complexes leads to the formation of alkenylpyrrole derivatives. Maximum yields of pyrrole adducts were obtained using *N*,*N*-dimethylhydrazones. A mechanism involving alkyne insertion followed by nucleophilic attack of the imine nitrogen at the intermediate alkenylcarbene complex was proposed.

In a recent publication, the coupling of Fischer carbene complexes (**1**, Scheme 1) with either enyne-aldehydes (e.g., **2**) or ketones to produce vinylfuran derivatives (e.g., **3**) was reported.[1] In a related study, the analogous preparation of vinylisobenzofurans from the coupling of Fischer carbene complexes with various *o*-alkynylbenzaldehyde derivatives was reported.[2] In this manuscript, extension of these studies to the preparation of pyrroles (e.g., **5**) from Fischer carbene complexes and enyne-imines (e.g., **4**) is reported.[3,4] In a process similar to that invoked for furan formation, coupling of enyne-imines with carbene complexes will afford vinylcarbene complex intermediate **6**, which can then undergo nucleophilic attack by nitrogen at the carbene carbon to afford pyrrole **5** (E-isomer)[5] after loss of chromium from intermediate **7**. Synthesis of pyrroles from imine-alkynes has precedent;[6] however, the conversion of **4** to **5** is unique in

Scheme 1



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[1] Herndon, J. W.; Wang, H. *J. Org. Chem.* **1998**, *63*, 4564−4565.

[2] (a) Ghorai, B. K.; Menon, S.; Johnson, D. L.; Herndon, J. W. *Org. Lett.* **2002**, *4*, 2121−2124. (b) Ghorai, B. K.; Herndon, J. W. *Org. Lett.* **2001**, *3*, 3535−3538. (c) Jiang, D.; Herndon, J. W. *Org. Lett.* **2000**, *2*, 1267−1269.

[3] Pyrrole syntheses based on the coupling of alkynes and carbene complexes have precedent; however, nitrogen is attached to the carbene in all cases. (a) Merlic, C. A.; Baur, A.; Aldrich, C. A. *J. Am. Chem. Soc.* **2000**, *122*, 7398−7399. (b) Parlier, A.; Rudler, M.; Rudler, H.; Goumont, R.; Daran, J. C.; Vaissermann, J. *Organometallics* **1995**, *14*, 2760−2774. (c) Grotjahn, D. B.; Kroll, F. E. K.; Schaefer, T.; Harms, K.; Dötz, K. H. *Organometallics* **1992**, *11*, 298−310. (d) Aumann, R.; Heinen, H.; Goddard, R.; Krueger, C. *Chem. Ber.* **1991**, *124*, 2587−2593. (e) Dragisich, V.; Murray, C. K.; Warner, B. P.; Wulff, W. D.; Yang, D. C. *J. Am. Chem. Soc.* **1990**, *112*, 1251−1253. (f) Dragisich, V.; Wulff, W. D.; Hoogsteen, K. *Organometallics* **1990**, *9*, 2867−2870.

[4] For an extensive listing of references to nitrogen heterocycle synthesis using carbene complexes, see: Kagoshima, H.; Akiyama, T. *J. Am. Chem. Soc.* **2000**, *122*, 11741−11742.

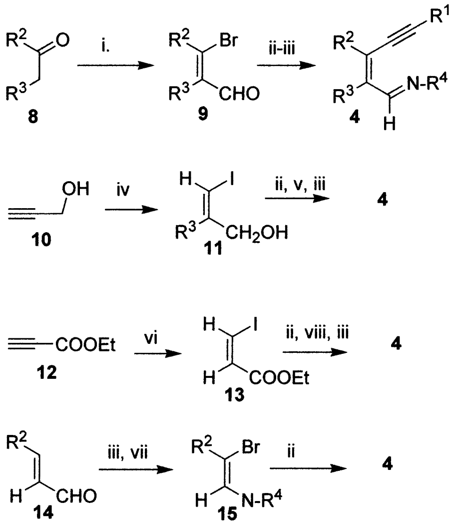
10.1021/ol034414j CCC: $25.00

that formation of an exocyclic carbon−carbon bond occurs simultaneously with closure of the pyrrole ring.

Prior to initiation of these studies, a concern was that direct coupling of the carbene complex and imine functionalities would interfere with the desired initial alkyne insertion. Previously reported ground-state reactions for imines and Fischer carbene complexes include aldol-like processes[7] and nucleophilic attack of the imine nitrogen at the carbene carbon.[8] Use of imines of minimal basicity (R^4 is electron-withdrawing) was initially deemed optimal because these side reactions would be less likely and these imines are electronically similar to the aldehyde carbonyl groups successfully employed in the furan synthesis. These compounds will be less optimal, however, in the key ring-closure step (conversion of **6** to **7**) because nucleophilicity at nitrogen is reduced. However, related compounds were found to be optimal for formation of pyrrolidine derivatives by intramolecular coupling of amines and group VI vinylidene complexes.[9]

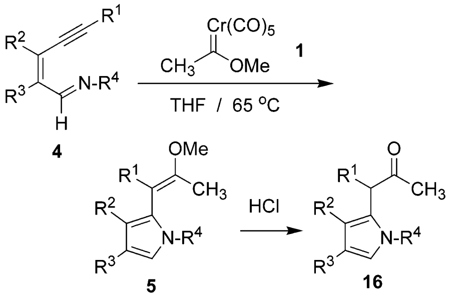
General synthetic protocols for the preparation of enyne-imines are depicted in Scheme 2. The choice of synthetic route for the preparation of enyne-imines **4** depends primarily on the identity of the R^2 and R^3 substituents. Compounds where R^2 and $R^3 \neq H$ or where R^2 = aryl, R^3 = H were prepared from ketones **8**.[10] Compounds where R^2 = alkyl and R^3 = H were prepared from α,β-unsaturated aldehydes **14**.[11] Compounds where R^2 = H and R^3 = alkyl/aryl were prepared from propargyl alcohol (**10**).[12] Compounds where R^2 and R^3 = H were prepared from ethyl propiolate (**12**).[13]

Scheme 2[a]



[a] (i) $PBr_3/DMF/CHCl_3$; (ii) $R^1C{\equiv}CH/(PPh_3)_2PdCl_2/CuI/Et_3N/THF$; (iii) R^4NH_2 (/$TiCl_4$ if R^4 = Ts); (iv) R^3MgBr/CuI, then I−Cl; (v) $ClCOCOCl/DMF/Et_3N/CH_2Cl_2$; (vi) NaI/HOAc; (vii) Br_2/CH_2Cl_2; (viii) DIBAL-H.

Scheme 3



A variety of imines were treated with carbene complex **1**; the results are depicted in Scheme 3 and Table 1. Initial studies focused on *N*-sulfonyl imines (entries B and C). The initially formed enol ether-pyrrole derivatives **5** were unstable with respect to air oxidation and were hydrolyzed to the corresponding ketones **16** for characterization purposes. Coupling of *N*-tosyl imine **4B** with methylcarbene complex **1** led to the desired pyrrole derivative **16B** in only 37% yield. The *N*-methanesulfonyl imine **4C** afforded a similar result. Electron-rich imines were next investigated as a result of the limited success using electron-deficient imines. The simple *N*-benzyl imine **4D** (entry D) was far less efficient and afforded pyrrole derivative in only 9% yield. No other identifiable products were obtained from these coupling reactions.

Table 1. Synthesis of Pyrroles through Coupling of Enyne-imines with Fischer Carbene Complexes

entry[a]	R^1	R^2	R^3	R^4	yield **16**[b] (%)
A	Bu	Ph	H	NMe_2	62
B	Bu	Ph	H	Ts	37
C	Bu	Ph	H	Ms	35
D	Bu	Ph	H	CH_2Ph	9
E	Bu	Bu	H	NMe_2	64
F	H	Bu	H	NMe_2	59[c]
G	Bu	H	H	NMe_2	70
H	Bu	H	Et	NMe_2	74
I	Bu	H	allyl	NMe_2	64
J	Bu	$-(CH_2)_4-$		NMe_2	36
K	Bu	$-(CH_2)_3-$		NMe_2	25[c]

[a] Table entry letters define substituents for compounds **4**−**16**. [b] Isolated yield of material that is pure by NMR and chromatographic analysis. [c] The hydrolysis step was omitted; the yield is for compound **5**.

Enyne-hydrazone derivatives of **4** were prepared so that imines at both extremes of the basicity scale could be evaluated.[14] Reactions employing this imine were far more efficient and led to the *N*-aminopyrrole derivatives. Coupling enyne-hydrazone with carbene complex **1** led to *N*-aminopyrrole derivative **16A** in considerably higher yield (entry A,

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(5) This stereochemistry is generally obtained in chromium carbene-alkyne couplings. McCallum, J. S.; Kunng, F. A.; Gilbertson, S. A.; Wulff, W. D. *Organometallics* **1988**, *7*, 2346−2360.

(6) (a) Arcadi, A.; Rossi, A. *Tetrahedron* **1998**, *54*, 15253−15272. (b) Knight, D.; Redfern, A. L.; Gilmore, J. *Chem. Commun.* **1998**, 2207−2208. (c) Kel'in, A.; Sromek, A. W.; Gevorgyan. V. *J. Am. Chem. Soc.* **2001**, *123*, 2074−2075.

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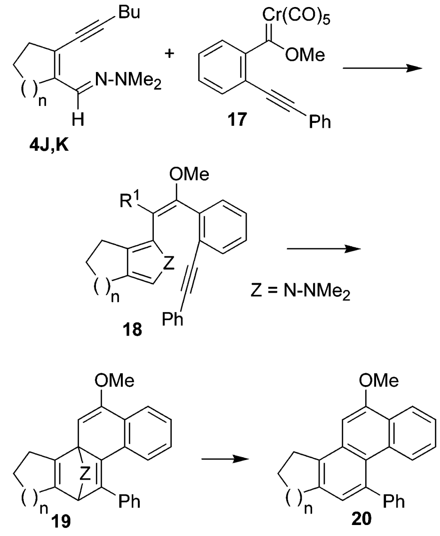
62%) than analogous imine derivatives in entries B−D. The imine nitrogen is far more basic and presumably more nucleophilic in this system. Stabilization of the carbene complex intermediate **6** by the amine nitrogen lone pair might also play a role in the higher yields obtained from the *N*,*N*-dimethylhydrazone.

Structurally diverse *N*,*N*-dimethylhydrazone derivatives of enyne **4** were prepared, and their subsequent reaction with carbene complex **1** was examined (entries E−K). The reaction appears to be quite general with respect to substitution on the alkene and alkyne and led to monosubstituted (entry G), 1,2-disubstituted (entries A, E, F), and 1,3-disubstituted (entries H and I) *N*-aminopyrrole derivatives in good yields. The trisubstituted *N*-aminopyrrole derivatives in entries J and K were obtained in considerably lower yield. These highly electron-rich compounds rapidly turned dark colors upon prolonged exposure to air, and thus the low yield in these cases might be attributed to product instability.

As a further test of the efficiency of pyrrole formation in entries J and K, the coupling of enyne-hydrazone **4K** with carbene complex **17**[15] was tested (Scheme 4). As expected, the initially formed pyrrole **18K** undergoes an intramolecular Diels−Alder reaction followed by aminonitrene extrusion[16] to afford the phenanthrene derivative **20K**. The reaction is quite efficient and affords dehydro-steroid product **20K** in 68% yield. The reaction employing the six-membered ring analogue **4J** proceeded similarly; however, the nitrogen bridge remained intact under the reaction conditions, leading to compound **19J** in 72% yield. The differing stability of the nitrogen bridge in compounds **19J** and **19K** is somewhat surprising. The efficient formation of **19J** and **20K** suggests that pyrrole formation in entries J and K is efficient and that the low yields are likely due to difficulty in isolating the extremely electron-rich pyrroles produced in these two examples.

Scheme 4



4,18-20: J, n = 2; **K**, n = 1

In conclusion, the conversion of enyne-imines (**4**) to pyrroles (**5**, **16**) has been demonstrated for a variety of substrates differing in the degree of alkyl substitution on the alkene and alkyne substituents. Optimal yields have been obtained using *N*,*N*-dimethylhydrazones. These reactions lead to *N*-aminopyrrole derivatives, which to date have been synthesized primarily from either reaction of 1,4-dicarbonyl derivatives with hydrazines[17] or from reaction of RCH═CH−N═N−COR derivatives with enolates.[18] *N*-Aminopyrrole derivatives have proven to be highly useful for cycloaromatization reactions[16] and can be converted to simple pyrroles through reduction.[19] Further investigation of the scope of this novel pyrrole-forming reaction and the synthetic potential of the pyrrole products is currently underway in this laboratory.

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Supporting Information Available: Detailed experimental for synthesis of compounds **4A−K**, **5F**, **5K**, **16A−E, 16G−J**, and **20K** and characterization data for compounds **5F**, **16A−E**, **16G−J**, **19J**, and **20K**. This material is available free of charge via the Internet at http://pubs.acs.org.

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