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Novel Synthesis of Isoquinolines Using Isobenzofuran–Nitrile Diels–Alder Reactions

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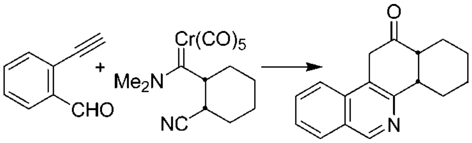
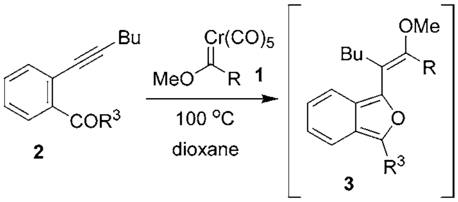
ABSTRACT



The synthesis of isoquinolines through coupling of 2-alkynylbenzaldehyde derivatives with *β*-cyanocarbene complexes has been examined. The reaction involves formation of an isobenzofuran followed by intramolecular Diels–Alder reaction with the nitrile, a process with limited precedent. The unique success of this process in this system has been attributed to deoxygenation of the initial adduct to form the isoquinoline ring system.

In this manuscript, successful trapping of carbene complex-derived isobenzofuran intermediates (e.g., **3**, Scheme 1)[1] through intramolecular Diels−Alder reaction with nitrile dienophiles is reported. Although nitrile−simple diene Diels−Alder reactions are known,[2] only one example of the Diels−Alder reaction between a nitrile and a furan/isobenzofuran has been reported.[3] The reverse reaction has ample precedent and is a key step in the synthesis of furans from oxazoles and alkynes.[4] Even isobenzofurans can be generated using a similar retro-Diels−Alder reaction, which occurs upon mild thermolysis.[5]

Scheme 1



The reaction under investigation involves the coupling of cyano-tethered carbene complexes (e.g., **4**, **6**, Scheme 2) with 2-alkynylbenzoyl derivatives (e.g., **2**). Several *β*-cyanocarbene complexes (**4**, **6**) were prepared through either (1) alkylation of simple carbene complexes (**1**) with bromoacetonitrile via the carbene complex-stabilized anion[6] (**4a**−**c**) or (2) treatment of acid chlorides or tertiary amides with $K_2Cr(CO)_5$ (**4d**,**e**, **6a**,**b**).[7] Overalkylation leading to dicyanocarbene complexes **4a**,**b** was a complication when using the simple methylcarbene complexes **1a**,**b**. Carbene complexes **4** and **6** are unstable in comparison with analogous complexes

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(1) (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. Lam, Y. F. *Org. Lett.* **2001**, *3*, 3535−3538. (c) Jiang, D.; Herndon, J. W. *Org. Lett.* **2000**, *2*, 1267−1269.

(2) Most examples involve electron-deficient nitriles. Recent examples include: (a) Volle, J. N.; Schlosser, M. *Eur. J. Org. Chem.* **2002**, 1490−1492. (b) Junge, H.; Oehme, G. *Tetrahedron* **1998**, *54*, 11027−11032.

(3) Diels−Alder adducts have only been characterized by combustion analysis and IR, and other structural alternatives were not considered. Tagmazyan, K. T.; Mkrtchyan, R. S.; Babayan, A. T. *J. Org. Chem. USSR* **1974**, *10*, 1657−1662.

(4) Hassner, A.; Fischer, B. *Heterocycles* **1993**, *35*, 1441−1465.

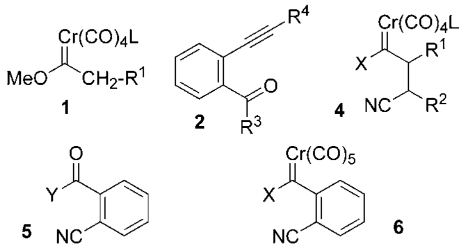
(5) Whitney, S. E.; Winters, M.; Rickborn, B. *J. Org. Chem.* **1990**, *55*, 929−935.

(6) For a related process using α-bromoesters, see: Casey, C. P.; Anderson, R. L. *J. Organomet. Chem.* **1974**, *73*, C28−C30.

(7) (a) Schwindt, M. A.; Lejon, T.; Hegedus, L. S. *Organometallics* **1990**, *9*, 2814−2819. (b) Semmelhack, M. F.; Lee, G. R. *Organometallics* **1987**, *6*, 1839−1844.

10.1021/ol035405d CCC: $25.00

Scheme 2



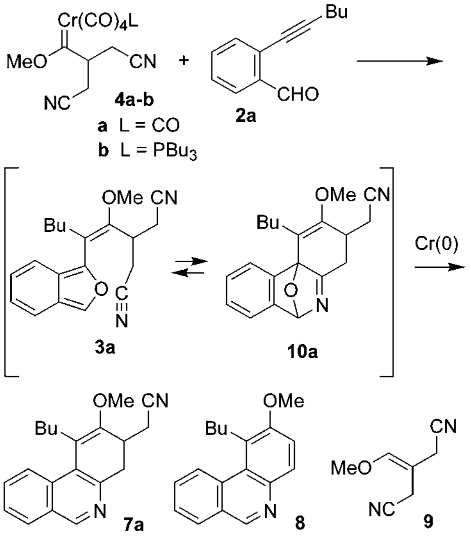
<u>complex 1</u>
a R^1 = H, L = CO
b R^1 = H, L = PBu_3
c R^1 = Pr, L = CO

<u>compound 2</u>
a R^3 = H, R^4 = Bu
b R^3 = Me, R^4 = Bu
c R^3 = Ph, R^4 = Bu
d R^3, R^4 = H

<u>complex 6</u>
a X = OMe
b X = NMe_2

<u>compound 4</u>
a R^1 = CH_2CN, R^2 = H, X = OMe, L = CO
b R^1 = CH_2CN, R^2 = H, X = OMe, L = PBu_3
c R^1 = *n*-Pr, R^2 = H, X = OMe, L = CO
d R^1,R^2 = -$(CH_2)_4$- (cis), X = OMe, L = CO
e R^1,R^2 = -$(CH_2)_4$- (cis), X = NMe_2, L = CO

Scheme 3

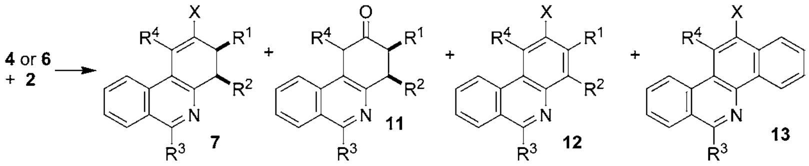


lacking a cyano group. Carbene complexes **4a** and **6a** are difficult to purify and decompose rapidly in the air. Aminocarbene complexes (**4e**, **6b**) and phosphine-substituted[8] complex **4b** were more stable than alkoxy pentacarbonylcarbene analogues.

Coupling of dicyanocarbene complex **4a** with alkyne-aldehyde **2a** was examined initially (Scheme 3 and Table 1, entry A). This coupling reaction afforded enol ether **9** (0−20% yield) and the isoquinoline derivatives **7a** and **8**. Enol ether **9** results from a known decomposition reaction of Fischer carbene complexes.[9] Formation of compound **7a** likely involves generation of isobenzofuran **3a** followed by intramolecular Diels−Alder reaction to afford adduct **10a**, which is deoxygenated to afford compound **7a**.[10] The origin of acetonitrile loss product **8** is unclear at present. Use of the phosphine analogue **4b** led to only **7a** and **8** (entry B); however, the ratio was different. The added stability of complex **4b** relative to **4a** likely suppresses decomposition.

Coupling of various *β*-cyanocarbene complexes with 2-alkynylbenzoyl derivatives has been examined (Table 1). Moderately efficient formation of the net dehydrogenation product **12c** was observed using the monocyanocarbene complex **1c** (entry C). The reaction was less efficient for formation of tetracyclic compound **7d** (entry D); however, the reaction process was considerably more efficient using the more stable aminocarbene complex **4e** (entry E), which afforded the ketone **11e** after enamine hydrolysis. The analogous reaction using ketone **2b** was also more efficient (entry F), possibly due to the increased stability of the isobenzofuran intermediate.[11] Benzo analogues were also tested (entries G−I). Similar trends were noted in the

Table 1. Synthesis of Isoquinolines



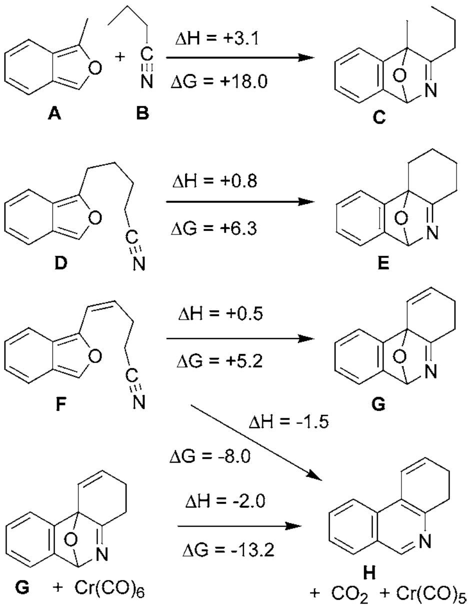
entry[a]	reactants	R^1	R^2	R^3	R^4	X	7	8	12	13
A	**4a** + **2a**	$-CH_2CN$	H	H	Bu	OMe	40%	36%		
B[b]	**4b** + **2a**	$-CH_2CN$	H	H	Bu	OMe	48%	19%		
C	**4c** + **2a**	−*n*-C_3H_7	H	H	Bu	OMe			53%	
D[c]	**4d** + **2d**	$R^{1,2} = -(CH_2)_4-$		H	H	OMe	21%			
E[c]	**4e** + **2d**	$R^{1,2} = -(CH_2)_4-$		H	H	NMe_2	42%[d]			
F	**4d** + **2b**	$R^{1,2} = -(CH_2)_4-$		Me	Bu	OMe	39%			
G	**6a** + **2a**			H	Bu	OMe				20%
H	**6b** + **2a**			H	Bu	NMe_2				40%
I	**6b** + **2c**			Ph	Bu	NMe_2				59%

[a] Table entry letters define substituents for compounds **3**, **7**, and **10**−**13**. [b] Product substituents identical to entry A; reported as **XXa**. [c] Toluene was used as the solvent. [d] Ketone **11e** was isolated.

formation of compound **13** in that higher yields were obtained using an aminocarbene complex (entry H) or if an isobenzofuran-stabilizing substituent (phenyl, entry I) is present.

A key step in the reactions in Table 1 is the Diels–Alder reaction between an isobenzofuran and a nitrile, which is not expected to be favorable.[4,5] The unique success of the nitrile–isobenzofuran Diels–Alder step in this reaction is likely due to either (1) an unusually favorable six-membered ring forming Diels–Alder reaction, or (2) equilibrium of **3a** and **10a** driven toward product formation through reductive removal of the oxygen bridge by chromium(0) byproducts. To better understand the factors favoring the key Diels–Alder step, the thermodynamic parameters of select reactions were evaluated using DFT calculations (Scheme 4, all values are in kcal/mol).[12] The isobenzofuran–nitrile Diels–Alder reaction is slightly endothermic in all examples depicted in Scheme 4; however, the entropic effects are less detrimental to the free energy of the intramolecular reactions. The experimental results in ref 5 further support the exergonic nature of isobenzofuran–nitrile Diels–Alder reactions. The deoxygenation process (conversion of **G** to **H**) using chromium hexacarbonyl as the hypothetical reducing agent is quite favorable, as is the overall conversion of isobenzofuran intermediate **F** to dihydrophenanthrene **H**. On the basis of the studies in Scheme 4, the success of this nitrile–isobenzofuran Diels–Alder reaction is most likely due to the presence of a suitable reductant, which drives the equilibrium toward cycloadduct formation through a deoxygenation–aromatization process.

Scheme 4



In summary, nitrile–isobenzofuran Diels–Alder reactions, a previously undocumented reaction process, can be useful for isoquinoline synthesis.[13] Efforts to further define the scope of this reaction using chromium carbene-based and other isobenzofuran generation methods are currently underway in this laboratory.

Acknowledgment. This work was supported by the National Science Foundation and the NIH SCORE Program. We are indebted to Prof. Haobin Wang of New Mexico State University for advice about the theoretical calculations.

Note Added after ASAP Posting. The β-CN substituent was missing in the carbene complex in the abstract and TOC graphic in the version posted ASAP October 11, 2003; the corrected version was posted October 27, 2003.

Supporting Information Available: Experimental details and spectra for reactions in Table 1 and carbene complex syntheses, as well as a discussion of calculations in Scheme 4. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) (a) McDonald, F. E.; Schultz, C. C.; Chatterjee, A. K. *Organometallics* **1995**, *14*, 3628–3629. (b) Aumann, R.; Hinterding, P. *Chem. Ber.* **1990**, *123*, 2047–2051. (c) Soderberg, B. C.; Turbeville, M. J. *Organometallics* **1991**, *10*, 3951–3953.

(10) Metal carbonyls perform similar reductions. Mitchell, R. H.; Ward, T. R. *Tetrahedron* **2001**, *57*, 3689–3695.

(11) For a review of isobenzofurans, see: Friedrichsen, W. *Adv. Heterocycl. Chem.* **1999**, *73*, 1–96.

(12) We are grateful to a reviewer for suggesting these studies.

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