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A Facile Method for the Synthesis of Polycyclic Indole Derivatives: The Generation and Reaction of Tungsten-Containing Azomethine Ylides

Hiroyuki Kusama, Jun Takaya, and Nobuharu Iwasawa*

Department of Chemistry, Tokyo Institute of Technology, O-okayama, Meguro-ku, Tokyo 152-8551, Japan

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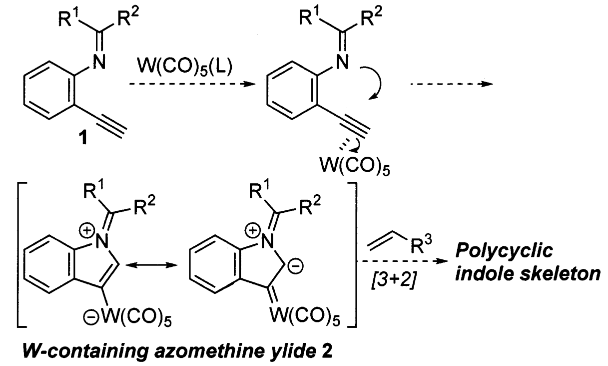
In this communication, we report a highly useful method for the construction of polycyclic indole derivatives through the [3 + 2] cycloaddition of novel, metal-containing azomethine ylides generated from *N*-(*o*-alkynylphenyl)imine derivatives and W(CO)$_5$(L).

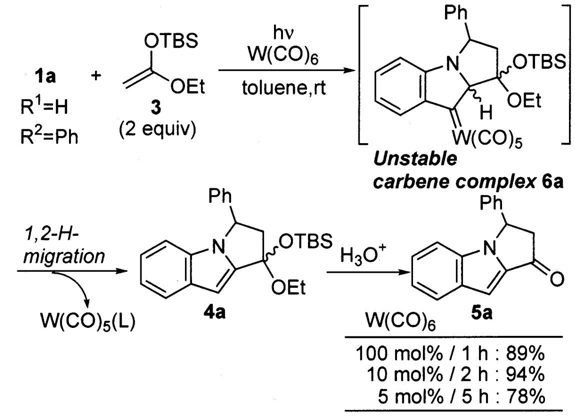
The indole skeleton is an important core framework for pharmaceuticals, insecticides, etc., and the development of novel, concise methods for the construction of polycyclic indole skeletons is strongly required.[1] We have considered the possibility of generating metal-containing azomethine ylides **2**,[2] having an indole nucleus, by the nucleophilic *endo*-attack of the imine nitrogen of the *N*-(*o*-alkynylphenyl)imine derivatives **1** onto their *ortho*-alkynyl group when activated by W(CO)$_5$.[3] The [3 + 2] cycloaddition of such ylides with electron-rich alkenes would afford a novel method for the construction of the polycyclic indole skeletons found in various biologically active molecules (Scheme 1).

Scheme 1



First, the aldimine **1a**, derived from *o*-ethynylaniline and benzaldehyde, was chosen as the precursor for generating a tungsten-containing azomethine ylide. Photoirradiation of a mixture of **1a**, ketene silyl acetal **3**, and a stoichiometric amount of W(CO)$_6$ in toluene at ambient temperature smoothly promoted the desired reaction to give a tricyclic indole derivative **5a** in 89% yield after acidic workup (Scheme 2). Furthermore, the same reaction, but using only a catalytic amount of W(CO)$_6$, also proceeded smoothly, affording the indole **5a** in high yield (10 mol %, 94%; 5 mol %, 78%).[4,5] We consider the mechanism of this reaction to be as follows: photoinduced dissociation of a carbonyl ligand from W(CO)$_6$ generates a coordinatively unsaturated, pentacarbonyltungsten species, which activates the alkyne moiety of **1a** electrophilically through π-complex formation.[6] The 5-*endo*, nucleophilic attack of the imine nitrogen onto this activated alkyne moiety generates a tungsten-containing azomethine ylide **2a**, which readily undergoes [3 + 2] cycloaddition with **3** to give an unstable tungsten carbene complex **6a**. Finally, 1,2-hydrogen migration to the carbene occurs, affording the product **4a** with regeneration of the pentacarbonyltungsten species (Scheme 2).

Scheme 2



As the desired reaction was found to proceed as expected, we next examined its generality by employing various imine derivatives and electron-rich alkenes (Table 1). Not only the ketene silyl acetal **3** but also mono- and disubstituted vinyl ethers (**7** and **8**, entries 1, 2), a trisubstituted enamine (**9**, entry 3), and 2-methoxyfuran (**10**, entry 4) reacted smoothly with the tungsten-containing azomethine ylide **2a** to afford the corresponding tri- or tetracyclic indole derivatives **11**−**14** as a mixture of diastereomers in good yield, even with a 10 mol % amount of W(CO)$_6$.[7] Furthermore, *N*-(*o*-ethynylphenyl)imidates **1b** and **1c** could also be employed as precursors of a tungsten-containing azomethine ylide reacting with the ketene silyl acetal **3** in the presence of W(CO)$_6$ under photoirradiation to give, after acidic workup, the corresponding indole derivatives **5b** and **5c** in moderate to good yield. The successful application of this methodology to such imidates is notable because the resulting indole derivatives possess an *N*,*O*-acetal, which should facilitate further functionalization of the products.[8]

Another novel aspect of this reaction was revealed during experiments using imine derivatives **15** containing an *internal* instead of terminal alkyne moiety. Thus, when a mixture of pentynyl derivative **15a** and *tert*-butyl vinyl ether **7** was treated with a stoichiometric amount of W(CO)$_6$ in toluene under photoirradiation for 1.5 h, the indole derivative **17a**, having a propyl group at the 3-position of the indole nucleus, was obtained as the major product, along with a small amount of a formal [4 + 2] adduct **18a** (Table 2, entry 1).[9] The formation of **17a** clearly indicates that 1,2-migration of the propyl group adjacent to the carbene carbon occurred on formation of the unstable carbene intermediate **16a**.

Furthermore, this type of 1,2-migration reaction also proceeded for substrates having a methyl or phenyl substituent on the alkyne

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* To whom correspondence should be addressed. E-mail: niwasawa@chem.titech.ac.jp.

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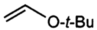
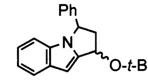
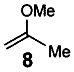
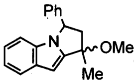
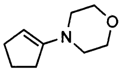
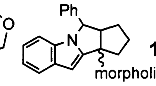
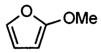
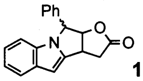
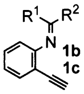
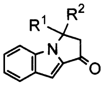
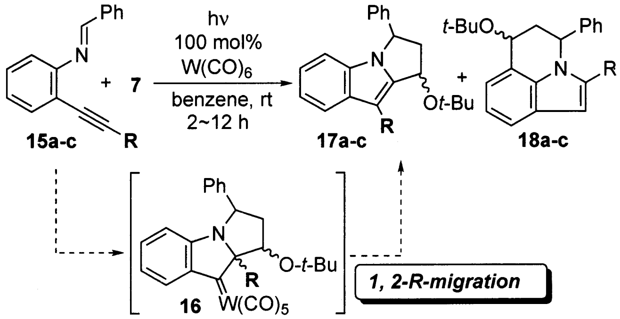
$$\text{imine} + \underset{(2\ \text{equiv})}{\text{alkene}} \xrightarrow[\substack{\text{toluene, room temperature} \\ 1.5-24\ \text{h}}]{\substack{h\nu \\ W(CO)_6}} \text{product}$$

Table 1. Reaction with Varioius Imines and Alkenes

Entry	Imine	Alkene	Product	Yield / % Loading of $W(CO)_6$ 100 mol%	10 mol%
1[a,b]	**1a**	 **7**	 **11**	52[d]	-
2[b]	**1a**	 **8**	 **12**	86[e]	66[f]
3	**1a**	 **9**	 **13**	67[g]	55[h]
4[b,c]	**1a**	 **10**	 **14**	74[i]	67[j]
	 **1b** : R^1=H, R^2=OEt **1c** : R^1=OMe, R^2=Me				
5[a,c]	**1b**	**3**	**5b**	74	68
6[a,c]	**1c**	**3**	**5c**	55	-

[a] In the presence of MS4A. [b] Ten equivalents of alkene was employed. [c] Acidic workup. [d] cis:trans = 86:14. [e] cis:trans = 44:56. [f] cis:trans = 46:54. [g] dr = 53:47. [h] dr = 54:46. [i] dr = 71:29. [j] dr = 77:23. (See Supporting Information for details of the stereochemistry.)

Table 2. Reactions with Internal Alkynes



entry	imine	**17**/%	**18**/%
1	R=Pr (**15a**)	76 (cis:trans = 22:78)	21 (dr = 94:6)
2	R=Me (**15b**)	55 (cis:trans = 25:75)	not detected
3	R=Ph (**15c**)	61 (cis:trans = 56:44)	14 (dr = 95:5)

terminus to give the corresponding substituted indole derivatives in good yield (Table 2, entries 2, 3). In the carbene complexes of group 6 metals, the facile 1,2-migration of hydrogen or even of a silicon group is well-precedented;[10] however, the 1,2-migration of an alkyl or an aryl group has only rarely been reported.[11,12] The facile 1,2-migration disclosed herein is probably facilitated by strong electron donation from the nitrogen atom to the σ^* orbital of the C−R bond in the carbene intermediate **16**. As a synthetic method, this protocol affords, in a single operation, the 6-5-5 tricyclic indole ring skeleton with a substituent at the 3-position of the indole nucleus, which is the basic structure of pharmaceutically valuable natural products such as mitomycin C.[13]

In summary, we have developed a novel method for the preparation of polycyclic indole derivatives employing tungsten-containing azomethine ylides generated from various *N*-(*o*-alkynylphenyl)imine derivatives and $W(CO)_5(L)$. These species readily undergo [3 + 2] cycloaddition with various electron-rich alkenes to give synthetically useful, polycyclic indole derivatives through 1,2-migration of a hydrogen, alkyl, or aryl substituent of the carbene intermediates.

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Supporting Information Available: Preparative methods and spectral and analytical data of compounds **1**−**18** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For recent examples of metal-catalyzed indole syntheses, see: (a) Hegedus, L. S. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1113. (b) Takeda, A.; Kamijo, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 5662 and references therein.
(2) For reviews on azomethine ylide, see: (a) Vedejs, E. *Advances in Cycloaddition*; JAI Press: Greenwich, CT, 1988; Vol. 1, pp 33−51. (b) Kanemasa, S.; Tsuge, O. *Advances in Cycloaddition*; JAI Press: Greenwich, CT, 1993; Vol. 3, pp 99−159. (c) Grigg, R.; Sridharan, V. *Advances in Cycloaddition*; JAI Press: Greenwich, CT, 1993; Vol. 3, pp 161−204. (d) Padwa, A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 4, pp 1069−1109.
(3) For our results on the generation and reaction of metal-containing carbonyl ylides, see: Iwasawa, N.; Shido, M.; Kusama, H. *J. Am. Chem. Soc.* **2001**, *123*, 5814.
(4) Initial cycloadduct **4a** was a mixture of two diastereomers (1:1).
(5) The reaction also proceeded using a catalytic amount of preformed $W(CO)_5$(thf) at room temperature to afford the same product **5a** in 75% yield after 7 days.
(6) For examples of electrophilic activation of alkynes with group 6 metals, including the formation of vinylidene complexes, see: (a) McDonald, F. E.; Chatterjee, A. K. *Tetrahedron Lett.* **1997**, *38*, 7687. (b) McDonald, F. E. *Chem.-Eur. J.* **1999**, *5*, 3103. (c) Cutchins, W. W.; McDonald, F. E. *Org. Lett.* **2002**, *4*, 749. (d) Miki, K.; Nishino, F.; Ohe, K.; Uemura, S. *J. Am. Chem. Soc.* **2002**, *124*, 5260. (e) Miura, T.; Iwasawa, N. *J. Am. Chem. Soc.* **2002**, *124*, 518 and references therein.
(7) Because the enamine moiety of the products **11** was fairly reactive as a dipolarophile, [3 + 2] cycloaddition between **11** and the ylide intermediate **2a** also proceeded to give 2:1 cycloadducts (see Supporting Information).
(8) For examples of Lewis acid-promoted, nucleophilic substitution reaction onto *N,O*-acetals, see: (a) Smith, A. B., III; Kanoh, N.; Ishiyama, H.; Hartz, R. A. *J. Am. Chem. Soc.* **2000**, *122*, 11254. (b) Sugiura, M.; Hagio, H.; Hirabayashi, R.; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 12510 and references therein.
(9) The formation of formal [4 + 2] cycloadducts can be explained by Diels−Alder reaction of the ylide intermediate with *tert*-butyl vinyl ether.
(10) For examples of the 1,2-migration of hydrogen or silicon groups in group 6 carbene complexes, see: (a) Dorwald, F. Z. *Metal Carbenes in Organic Synthesis*; Wiley-VCH: Weinheim, 1999. (b) Iwasawa, N.; Saitou, M.; Kusama, H. *J. Organomet. Chem.* **2001**, *617−618*, 741 and references therein.
(11) 1,2-Alkyl migration of group 6 metal carbene intermediates is reported in a few, specific cases. See: (a) Zora, M.; Herndon, J. W.; Li, Y.; Rossi, J. *Tetrahedron* **2001**, *57*, 5097 and references therein. (b) Nagao, K.; Chiba, M.; Kim, S.-W. *Synthesis* **1983**, 197.
(12) For other examples of 1,2-alkyl migration in carbene complexes of the late transition metals, see ref 10a. See also: Bly, R. S.; Bly, R. K.; Hossain, M. M.; Lebioda, L.; Raja, M. *J. Am. Chem. Soc.* **1988**, *110*, 7723.
(13) For examples of the synthesis of mitomycin C and its analogues, see: (a) Remers, W. A.; Iyenger, B. S. *Recent Prog. Chem. Synth. Antibiot.* **1990**, 415. (b) Michael, J. P.; Koning, C. B.; Petersen, R. L.; Stanbury, T. V. *Tetrahedron Lett.* **2001**, *42*, 7513 and references therein.

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