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A Novel Approach to 2-Arylated Quinolines: Electrocyclization of Alkynyl Imines via Vinylidene Complexes

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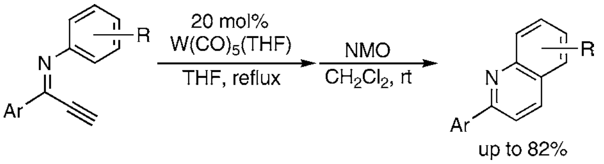
ABSTRACT



Alkynyl imines underwent [4 + 2] electrocyclization in the presence of 20 mol % $W(CO)_5(THF)$ to give 2-arylated quinolines in good yields. A deuterium labeling study suggests that the reaction proceeds via a tungsten vinylidene complex.

Quinoline skeletons play important roles as components of biologically active compounds.[1] In particular, 2-arylated quinolines are naturally present and occur in structures of 5-lipoxygenase inhibitors,[2] leucotriene antagonists,[3] LTD_4 receptor antagonists,[4] and other biologically active molecules.

Although a variety of condensation reactions such as the Skraup synthesis were reported for quinoline construction,[5] development of novel and expeditious methods is still desired.[6]

As a part of our continuing interest in the reaction of imines and group 6 metal complexes,[7] we recently found a novel catalytic electrocyclization method of *N*-aryl alkynyl imines. In this communication, we describe a novel quinoline synthesis that proceeds via catalytically generated tungsten vinylidene complexes.

At first, we examined the reaction of $M(CO)_6$ (M = Cr, Mo, W) and an alkynyl imine. A mixture of an alkynyl imine **1a** and an equimolar amount of $M(CO)_6$ was irradiated in toluene for 9–10 h, and the reaction mixtures were purified by preparative TLC to give 2-phenylquinoline **2a** (Table 1, entries 1–3). Among the three metals examined, $W(CO)_6$ gave the most favorable result (34% yield, entry 3). Further optimization of the reaction conditions revealed that use of $W(CO)_5(THF)$[8] and THF as a solvent increased the yield up to 52% (entry 5).

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[1] (a) Michael, J. P. *Nat. Prod. Rep.* **2001**, *18*, 543. (b) Funayama, S.; Murata, K.; Noshita, T. *Heterocycles* **2001**, *54*, 1139.

[2] Musser, J. H,; Chakraborty, U. R.; Sciortino, S.; Gordon, R. J.; Khandwala, A.; Neiss, E. S.; Pruss, T. P.; Van Inwegen, R.; Weinryb, I.; Coutts, S. M. *J. Med. Chem.* **1987**, *30*, 96.

[3] Van Inwegen, R. G.; Khandwala, A.; Gordon, R.; Sonnino, P.; Coutts, S.; Jolly, S. *J. Pharm. Exp. Therapeut.* **1987**, *24*, 117.

[4] Gauthier, J. Y.; Jones, T.; Champion, E.; Charette, L.; Dehaven, R.; Ford-Hutchinson, A. W.; Hoogsteen, K.; Lord, A.; Masson, P.; Piechuta, H.; Pong, S. S.; Springer, J. P.; Therien, M.; Zamboni, R.; Young, R. N. *J. Med. Chem.* **1990**, *33*, 2841.

[5] Jones, G. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, A. R., Eds.; Pergamon: New York, 1984; Vol. 2, p 395.

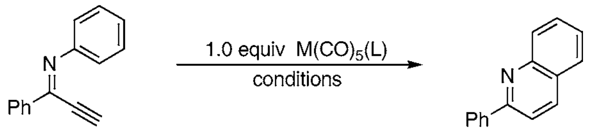
[6] Recent transition metal-catalyzed synthetic methods: (a) Amii, H.; Kishikawa, Y.; Uneyama, K. *Org. Lett.* **2001**, *3*, 1109. (b) Mahanty, J. S.; De, M.; Das, P.; Kundu, N. G. *Tetrahedron* **1997**, *53*, 13397. (c) Takahashi, T.; Li, Y.; Stepnicka, P.; Kitamura, M.; Liu, Y.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **2002**, *124*, 576. (d) Cho, C. S.; Kim, B. T.; Kim, T.-J.; Shim, S. C. *Chem. Commun.* **2001**, 2576 and references therein.

[7] Our recent reports on reactions of group 6 metal carbene complexes with imines: (a) Kagoshima, H.; Akiyama, T. *J. Am. Chem. Soc.* **2000**, *122*, 11741. (b) Kagoshima, H.; Okamura, T.; Akiyama, T. *J. Am. Chem. Soc.* **2001**, *123*, 7182. (c) Sangu, K.; Kagoshima, H.; Fuchibe, K.; Akiyama, T. *Org. Lett.* **2002**, *4*, 3967.

[8] $W(CO)_5(THF)$ was prepared just before use by irradiating a slurry of $W(CO)_6$ in dry THF under Ar for 2 h using a high-pressure mercury lamp (450W).

10.1021/ol036190a CCC: $27.50

Table 1. Examination of Reaction Conditions



1a **2a**

entry	M(CO)$_5$(L)	conditions	yield/%
1	Cr(CO)$_6$	toluene, $h\nu$, rt, 10 h	18
2	Mo(CO)$_6$	toluene, $h\nu$, rt, 9 h	13
3	W(CO)$_6$	toluene, $h\nu$, rt, 9 h	34
4	W(CO)$_6$	THF,$h\nu$, rt, 9 h	16
5	W(CO)$_5$(THF)	THF, reflux, 3 h	52

Oxidative treatment of the crude mixture improved the yield. Thus, after the reaction had completed, the crude mixture was treated with 3 molar amounts of NMO (*N*-methylmorpholine *N*-oxide) in dichloromethane at room temperature for 1 h and purified by preparative TLC to give **2a** in 70% yield (Scheme 1).[9] Furthermore, this reaction proceeded even with 20 mol % W(CO)$_5$(THF), although the rate of the reaction decreased (60% yield, 24 h).

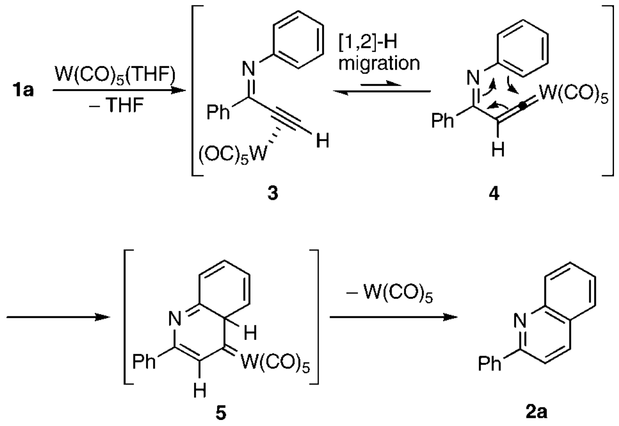
Scheme 1

$$\mathbf{1a} \xrightarrow[\text{THF, reflux}]{\text{W(CO)}_5\text{(THF)}} \xrightarrow[\text{CH}_2\text{Cl}_2\text{, rt, 1 h}]{\text{3.0 equiv } \textbf{\textit{NMO}}} \mathbf{2a}$$

1.0 equiv of W(CO)$_5$(THF); **70%**
0.2 equiv of W(CO)$_5$(THF); **60%**

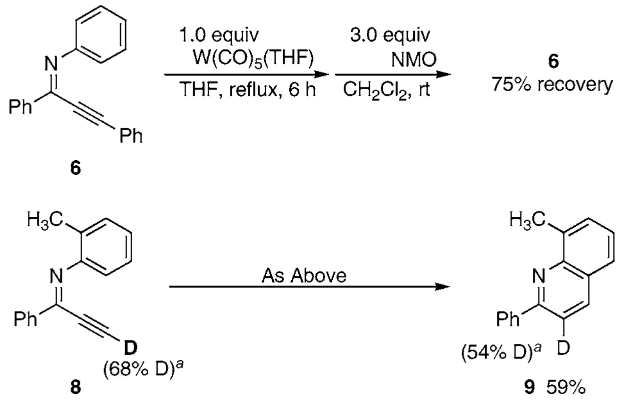
Presumably, this reaction proceeds as follows (Scheme 2): alkynyl imine **1a** complexes with W(CO)$_5$(THF) to generate π-alkyne complex **3**, which reversibly produces vinylidene complex **4** by [1,2]-hydrogen migration.[10] Subsequently, electrocyclization of **4** takes place to give unstable tungsten carbene complex **5**, which gives **2a** and regenerates W(CO)$_5$.

Scheme 2



Although it was quite difficult to isolate or capture the vinylidene intermediate **4**, experimental results described below (Scheme 3) support the [1,2]-hydrogen migration–vinylidene formation mechanism. First, phenyl-ethynyl imine **6** did not react under the reaction conditions and was recovered in 75% yield. Second, deuterated alkynyl imine **8** gave 3-deuterated quinoline **9** in 59% yield.

Scheme 3



[a] Deuterium incorporation was determined by relative intensity on mass spectroscopy.

Under the optimized conditions described in Scheme 1,[11] we examined the generality of this reaction (Table 2). Alkynyl imines **1b** and **1c** possessing electron-donating substituents on the aniline ring provided **2b** and **2c** in good yields. Imines **1d** and **1e** bearing electron-withdrawing substituents on the aniline ring afforded **2d** and **2e** in moderate yields.

This reaction could be applied not only to para-substituted substrates such as **1a–e** but also to ortho- and meta-

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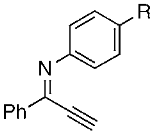
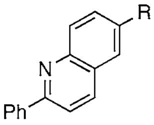
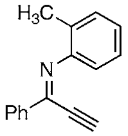
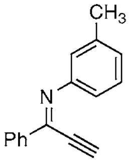
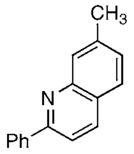
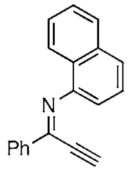
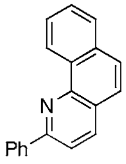
(9) This fact suggests that tungsten was complexed to **2a** and was lost during workup or purification.

(10) For reviews on vinylidene complexes, see: (a) Bruneau, C.; Dixneuf, P. H. *Acc. Chem. Res.* **1999**, *32*, 311. (b) Bruce, M. I. *Chem. Rev.* **1991**, *91*, 197. (c) Bruce, M. I.; Swincer, A. G. *Adv. Organomet. Chem.* **1983**, *22*, 59. For synthetic use of vinylidene intermediates of group 6 metals, see for examples: (d) McDonald, F. E.; Schultz, C. C. *J. Am. Chem. Soc.* **1994**, *116*, 9363. (e) McDonald, F. E. *Chem. Eur. J.* **1999**, *5*, 3103. (f) Maeyama, K.; Iwasawa, N. *J. Am. Chem. Soc.* **1998**, *120*, 1928. (g) Maeyama, K.; Iwasawa, N. *J. Org. Chem.* **1999**, *64*, 1344. (h) Iwasawa, N.; Maeyama, K.; Kusama, H. *Org. Lett.* **2001**, *3*, 3871. (i) Kusama, H.; Yamabe, H.; Iwasawa, N. *Org. Lett.* **2002**, *4*, 2569. (j) Iwasawa, N.; Shido, M.; Maeyama, K.; Kusama, H. *J. Am. Chem. Soc.* **2000**, *122*, 10226. (k) Miura, T.; Iwasawa, N. *J. Am. Chem. Soc.* **2002**, *124*, 518. (l) Miki, K.; Nishino, F.; Ohe, K.; Uemura, S. *J. Am. Chem. Soc.* **2002**, *124*, 5260 and references therein.

(11) **Typical Procedure.** A slurry of tungsten hexacarbonyl (70 mg, 0.20 mmol) in dry THF (2 mL) was irradiated for 2 h using a high-pressure mercury lamp (450W). To the resulting yellow solution was added **1a** (41 mg, 0.20 mmol) in THF (1 mL), and the solution was refluxed for 2 h. After confirmation that alkynyl imine **1a** was consumed completely by TLC analysis, the solvent was removed in vacuo and a solution of NMO (70 mg, 0.60 mmol) in dichloromethane was added and stirred at room temperature for 1 h. The reaction mixture was filtered through a small pad of silica gel using ethyl acetate as an eluent. The filtrate was concentrated and purified by preparative TLC (silica gel, 10:1 hexane/ethyl acetate) to afford the quinoline derivative **2a** as a yellow solid (28.6 mg, 70%).

Table 2. Reaction with Various Alkynyl Imines (**1**)

$$\text{alkynyl imine } \mathbf{1} \xrightarrow[\text{THF, reflux, 1–3 h}]{\text{x equiv W(CO)}_5\text{(THF)}} \xrightarrow[\text{CH}_2\text{Cl}_2\text{, rt, 1 h}]{\text{3.0 equiv NMO}} \text{product(s)}$$

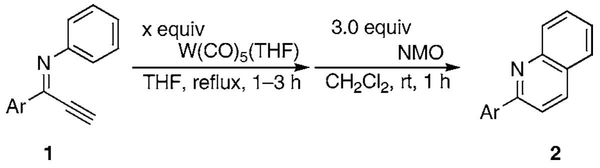
alkynyl imine	product(s)	yield/%	
		x = 1.0	0.2 [a]
			
1a R = H	**2a**	70	69, 65 [b]
1b R = OCH_3	**2b**	69	71
1c R = CH_3	**2c**	70	69
1d R = Cl	**2d**	45	
1e R = F	**2e**	47	
 **1f**	 **2f**	73	70
 **1g**	 **2g**	71 [c]	65 [c]
 **1h**	 **2h**	79	82

[a] Reaction was carried out over 24 h. [b] Reaction was carried out in a scale 25 times larger than usual. **1a** was recovered in 12% yield. [c] Products were obtained as 97/3 regioisomeric mixtures.

substituted substrates: reaction of *o*-tolyl alkynyl imine **1f** afforded the corresponding quinoline **2f** in 73% yield. The *m*-tolyl substrate **1g** gave the corresponding product **2g** as a 97/3 regioisomeric mixture, which is apparently due to steric effects. Furthermore, *N*-(1-naphthyl) alkynyl imine **1h** worked well to give the corresponding benzoquinoline derivative **2h** in 82% yield.

Finally, we examined the generality on imine carbon (Table 3). Alkynyl imines **1i**−**l**, which possess electron-donating and electron-withdrawing groups on the benzylidene ring, afforded the corresponding 2-arylated quinoline derivatives in good yields.[12,13]

Table 3. Reaction with Various Alkynyl Imines (**2**)



entry	Ar	yield (%)	
		x = 1.0	*x* = 0.2[a]
1	Ph (**1a**)	70	60
2	*p*-$CH_3OC_6H_4$ (**1i**)	65	61
3	*p*-$CH_3C_6H_4$ (**1j**)	71	68
4	*m*-$CH_3C_6H_4$ (**1k**)	67	63
5	*p*-ClC_6H_4 (**1l**)	63	58

[a] Reaction was carried out over 24 h.

In summary, we have developed a novel synthesis of 2-substituted quinoline derivatives utilizing electrocyclization of alkynyl imines via tungsten vinylidene complex.

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Supporting Information Available: Spectral data (^{1}H NMR, ^{13}C NMR, IR, and elemental analysis) for all of the products listed in Tables 2 and 3. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) *N*-[1-(2-Methylphenyl)prop-2-yn-1-ylidene]aniline (ortho isomer of compound **1j**) afforded the corresponding quinoline derivative in 21% yield under the reaction conditions. Steric hindrance of the methyl group might decrease the planarity of the vinylidene intermediate and retard the electrocyclization step.

(13) Reactions of alkyl- or alkenyl-substituted alkynyl imines (not aryl alkynyl imines) have not been examined yet due to their difficulties of preparation.