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

Kenichiro Sangu, Kohei Fuchibe, and Takahiko Akiyama*

Department of Chemistry, Faculty of Science, Gakushuin University, 1-5-1 Mejiro Toshima-ku, Tokyo 171-8588, Japan

takahiko.akiyama@gakushuin.ac.jp

Received November 7, 2003

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 LTD₄ 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.

ORGANIC LETTERS

2004 Vol. 6, No. 3

353-355

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).

^{(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).

Table 1. Examination of Reaction Conditions

Ph 1	1.0 eo	uiv M(CO)₅(L) conditions Ph´	2a
entry	M(CO) ₅ (L)	conditions	yield/%
1	Cr(CO) ₆	toluene, <i>hv</i> , rt, 10 h	18
2	Mo(CO) ₆	toluene, <i>hv</i> , rt, 9 h	13
3	W(CO) ₆	toluene, <i>hv</i> , rt, 9 h	34
4	W(CO) ₆	THF, <i>hv</i> , 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).



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 Sub-

sequently, electrocyclization of 4 takes place to give unstable tungsten carbene complex 5, which gives 2a and regenerates $W(CO)_5$.

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—



^{*a*} Deuterium incorporation was determined by relative intensity on mass spectroscopy.

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.

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-

⁽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. 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%).



^{*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-

Ar	x equiv W(CO)₅(THF) THF, reflux, 1–3 h	3.0 equiv NMO CH ₂ Cl ₂ , rt, 1 h	Ar	
1			2	
		yie	yield (%)	
entry	Ar	x = 1.0	$x = 0.2^{a}$	
1	Ph (1a)	70	60	
2	<i>p</i> -CH ₃ OC ₆ H ₄ (1i)	65	61	
3	$p-CH_{3}C_{6}H_{4}(1)$	71	68	
4	<i>m</i> -CH ₃ C ₆ H ₄ (1k)	67	63	
		00	50	

donating and electron-withdrawing groups on the benzylidene ring, afforded the corresponding 2-arylated quinoline derivatives in good yields.^{12,13}

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

Acknowledgment. This work was supported by a Grantin-Aid for Scientific Reseach on Priority Areas (A) "Exploitation of Multi-Element Cyclic Molecules" from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

Supporting Information Available: Spectral data (¹H NMR, ¹³C 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.

OL036190A

⁽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.