

Iridium-Catalyzed Annulation of *N*-Arylcarbamoyl Chlorides with Internal Alkynes

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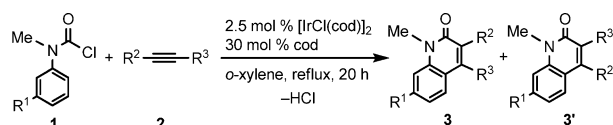
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Abstract: An iridium complex successfully catalyzed the annulation of various *N*-arylcarbamoyl chlorides with internal alkynes to afford 2-quinolones in good to excellent yields. The present reaction is widely applicable to substrates with various functionalities. An amide–iridacycle complex was isolated, and it is likely that such an iridacycle species is a key intermediate in the catalytic reaction.

The large number of carbonyl-containing *N*-heterocycles in biologically active molecules have motivated many efforts for their synthesis and functionalization.¹ The transition-metal-catalyzed intermolecular reaction of carbonyl precursors with alkynes is one of the most straightforward methods for constructing cyclic carbonyl compounds.^{2–4} On the other hand, carbamoyl chlorides are useful substrates for introducing amide functionality in organic synthesis, and they are mainly utilized in transition-metal-catalyzed reactions as coupling reagents.⁵ We considered that *N*-arylcarbamoyl chloride, in particular, would be a promising substrate for providing 2-quinolones^{6–8} via transition-metal-catalyzed annulation with alkynes. To realize this transformation, facile decarbonylation^{9,10} from the putative acylmetal species must be suppressed in the catalysis. We recently reported the iridium-catalyzed addition of acid chlorides to alkynes^{11a} and the palladium-catalyzed addition of formamides to alkynes^{11b} by suppressing the decarbonylation. Herein we report that the annulation of *N*-arylcarbamoyl chlorides (**1**) with internal alkynes (**2**) to afford 2-quinolones proceeds efficiently in the presence of an iridium complex.

First, *N*-methyl-*N*-phenylcarbamoyl chloride (**1a**) was reacted with 5-decyne (**2a**) in the presence of a catalytic amount (2.5 mol %) of [IrCl(cod)]₂ (cod = 1,5-cyclooctadiene) and 30 mol % added cod.¹² Reaction in refluxing *o*-xylene for 20 h afforded 3,4-dibutyl-1-methyl-2-quinolone (**3aa**) in 92% yield (Table 1, entry 1). Reaction in refluxing toluene also provided **3aa** in 82% yield. However, with PPh₃ as an additive, the yields of **3aa** decreased to 52% (P/Ir = 1) and 25% (P/Ir = 2) in refluxing toluene. Addition of bases such as Na₂CO₃ and *N*(*i*-Pr)₂Et to scavenge the evolved HCl did not affect the reaction at all. Various aliphatic and aromatic internal alkynes (**2b–i**) afforded the corresponding 2-quinolones. Importantly, no indole derivatives produced by decarbonylation were obtained during the reaction. 1,4-Dimethoxy-2-butyne (**2b**) and diphenylacetylene (**2c**) reacted with **1a** to give **3ab** and **3ac**, respectively, in good yields (entries 2 and 3). Diarylalkynes **2c–e** successfully reacted with *N*-(3-methoxyphenyl)-*N*-methylcarbamoyl chloride (**1b**) to give **3bc–be** in high yields, notably as single regioisomers (entries 4–6). Unsymmetrical alkynes 1-cyclohexyl-1-propyne (**2f**) and 1-phenyl-1-propyne (**2g**) reacted smoothly with **1a** to afford **3af** and **3ag**, respectively, in high yields, albeit with low regioselectivities (entries 7 and 8). The use of unsymmetrical alkynes bearing ether functionality (**2h** and **2i**) improved

Table 1. Iridium-Catalyzed Reaction of **1** with **2**^a

					
entry	1: R ¹	2: R ² , R ³	3	yield (%) ^b	3/3' ^c
1	1a : H	2a : Bu, Bu	3aa	92 (82) ^d	—
2	1a : H	2b : MeOCH ₂ , MeOCH ₂	3ab	62	—
3	1a : H	2c : Ph, Ph	3ac	67 ^e	—
4	1b : MeO	2c : Ph, Ph	3bc	82 ^e	—
5	1b : MeO	2d : 4-MeOC ₆ H ₄ , 4-MeOC ₆ H ₄	3bd	89 ^e	—
6	1b : MeO	2e : 4-ClC ₆ H ₄ , 4-ClC ₆ H ₄	3be	76 ^e	—
7	1a : H	2f : Me, Cy	3af	89	55/45
8	1a : H	2g : Ph, Me	3ag	95	58/42
9	1a : H	2h : MeOCH ₂ , <i>n</i> -C ₅ H ₁₁	3ah	91	72/28
10	1a : H	2i : Me, 2-MeOC ₆ H ₄	3ai	69	82/18

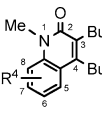
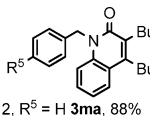
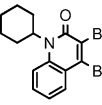
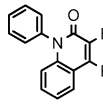
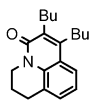
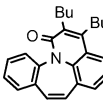
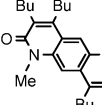
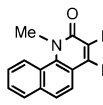
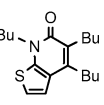
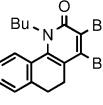
^a Conditions: **1** (0.50 mmol), **2** (1.0 mmol), [IrCl(cod)]₂ (0.0125 mmol, 2.5 mol %), and cod (0.15 mmol, 30 mol %) in refluxing *o*-xylene (1.0 mL) for 20 h. ^b Isolated yields of **3** and **3'**. ^c The **3/3'** ratio was determined by GC. ^d In refluxing toluene. ^e [IrCl(cod)]₂ (0.025 mmol, 5.0 mol %), cod (0.50 mmol, 100 mol %).

the regioselectivity of the products (**3ah** and **3ai**), possibly as a result of the directing effect of the oxygen atom (entries 9 and 10). Terminal alkynes such as 1-decyne and phenylacetylene did not afford **3**.

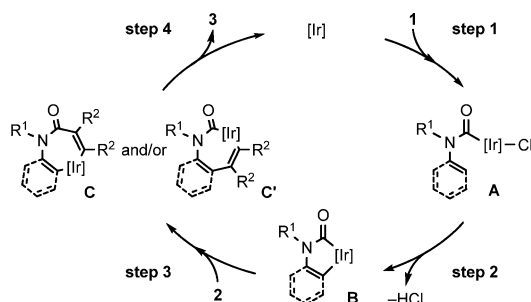
A wide variety of carbamoyl chlorides (**1**) can easily be synthesized from the corresponding amines.¹³ Various carbamoyl chlorides (**1b–v**)¹² thus obtained were reacted with **2a**, as shown in Table 2. Electron-rich (**1b–f**) and electron-poor (**1g–l**) phenyl moieties on the nitrogen smoothly participated in the cyclization to afford **3ba–fa** (entries 1–5) and **3ga–la** (entries 6–11) in good to excellent yields. Again, the cyclization of **1b** and **1e** was regioselective, affording **3ba** and **3ea**, respectively, as single isomers (entries 1 and 4). *N*-Phenylcarbamoyl chlorides bearing benzyl (**1m**), 4-methoxyphenylmethyl (**1n**), cyclohexyl (**1o**), and phenyl (**1p**) substituents on the nitrogen atom afforded the corresponding 2-quinolones (**3ma–pa**) in good to excellent yields (entries 12–15). The 4-methoxyphenylmethyl group of **3na** (entry 13) was removed by treatment with trifluoroacetic acid, affording 3,4-dibutyl-2-quinolone in 91% yield.¹² Condensed ring systems (**3qa–ta**) were constructed using **1q–t** (entries 16–19). Besides 2-quinolones, *N*-butyl-*N*-2-thienylcarbamoyl chloride (**1u**) afforded the corresponding product **3ua** in excellent yield (entry 20). It is worth noting that the reaction could be applied not only to *N*-aryl-substituted carbamoyl chlorides but also to *N*-alkenyl-substituted **1v**, which provided the corresponding pyridone derivative **3va** in 52% yield (entry 21).

To gain further insight into the mechanism of the catalytic reaction, stoichiometric reactions between [IrCl(cod)]₂ and **1a** were carried out in the presence of added cod (eqs 1 and 2). After 12 h, **1a** was converted completely in refluxing toluene. When **2a** was then added to the reaction mixture under reflux, **3aa** was obtained

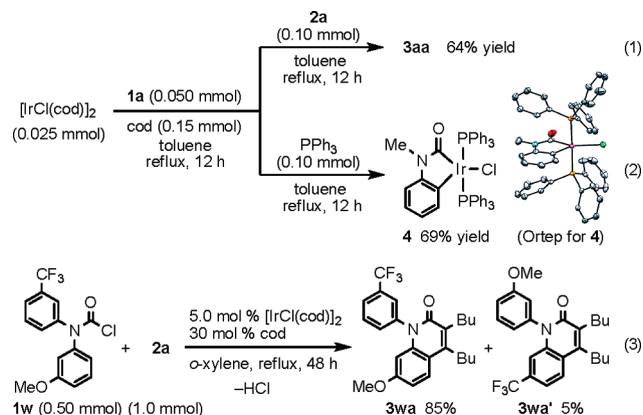
Table 2. Synthesis of **3** from **1** and **2a** (entry, product, yield)^{a,b}

 1, R ⁴ = 7-OMe 3ba , 85% 2, R ⁴ = 6-OMe 3ca , 89% 3, R ⁴ = 8-Me 3da , 86% 4, R ⁴ = 7-Me 3ea , 93% 5, R ⁴ = 6-Me 3fa , 91% 6, R ⁴ = 6-Cl 3ga , 87% 7, R ⁴ = 6-Br 3ha , 57% ^c 8, R ⁴ = 6-CF ₃ 3ia , 82% ^c 9, R ⁴ = 6-CO ₂ Me 3ja , 80% 10, R ⁴ = 6-NO ₂ 3ka , 73% 11, R ⁴ = 6-CN 3la , 59% ^c 12, R ⁵ = H 3ma , 88% 13, R ⁵ = OMe 3na , 66%	 12, R ⁵ = H 3ma , 88% 13, R ⁵ = OMe 3na , 66%		
 14, 3oa , 81%	 15, 3pa , 88% ^{c,d}	 16, 3qa , 51%	 17, 3ra , 70%
 18, 3sa , 68% ^e	 19, 3ta , 90%	 20, 3ua , 99%	 21, 3va , 52% ^{c,f}

^a Conditions: **1** (0.50 mmol), **2a** (1.0 mmol), [IrCl(cod)]₂ (0.0125 mmol, 2.5 mol %), and cod (0.15 mmol, 30 mol %) in refluxing *o*-xylene (1.0 mL) for 20 h. ^b Isolated yields. ^c [IrCl(cod)]₂ (0.025 mmol, 5.0 mol %). ^d For 36 h. ^e **1s** (0.25 mmol), **2a** (1.0 mmol), [IrCl(cod)]₂ (0.0125 mmol, 5.0 mol %), cod (0.15 mmol, 60 mol %). ^f For 48 h.

Scheme 1. Plausible Reaction Mechanism

in 64% yield (eq 1). In eq 1, however, no iridium complexes were identified. Therefore, instead of **2a**, PPh₃ (P/Ir = 2) was added into the reaction mixture (eq 2). As a result, iridium(III) metallacycle complex **4** was isolated in 69% yield, and the structure of **4** was confirmed by X-ray diffraction.¹² Iridacycle **4** did not provide **3aa** either catalytically or in a stoichiometric reaction with **2a** in refluxing toluene or xylene. As for the cyclization, **1w** having both the 3-methoxyphenyl and 3-trifluoromethylphenyl moieties was reacted with **2a** (eq 3). The cyclization occurred preferentially at the more-electron-rich phenyl ring (**3wa/3wa'** = 17/1).



A plausible reaction mechanism is shown in Scheme 1. Oxidative addition of **1** to the iridium(I) species (step 1) occurs, generating the

carbamoylchloroiridium(III) intermediate **A**.¹⁴ Next, an intramolecular cyclization (step 2) affords five-membered iridacycle **B**.¹⁵ The relevant complex **4** was isolated with the aid of PPh₃ coordination in eq 2. The cyclization must be electrophilic, since **3wa** was preferentially obtained over **3wa'** in eq 3. The construction of the iridacycle **B** would play a crucial role in suppressing the decarbonylation. Subsequent insertion of **2** (step 3) followed by reductive elimination (step 4) affords the 2-quinolone and regenerates the iridium(I) species.

In conclusion, 2-quinolones have been successfully obtained by iridium-catalyzed annulation of *N*-arylcabamoyl chlorides (**1**) with internal alkynes (**2**). It is likely that iridacycle **B** is a key intermediate in the catalytic reaction. Further studies of the reaction mechanism and application of the catalysis are now in progress.

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Supporting Information Available: Experimental procedures, characterization of the products, and crystallographic data (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1) (a) Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles*; Wiley-VCH: Weinheim, Germany, 2003. (b) Costero, A. M. *Adv. Heterocycl. Chem.* **1993**, *58*, 171.
- (2) For selected examples, see: (a) Guimond, N.; Gouliaras, C.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 6908. (b) Perreault, S.; Rovis, T. *Chem. Soc. Rev.* **2009**, *38*, 3149. (c) Satoh, T.; Ueura, K.; Miura, M. *Pure Appl. Chem.* **2008**, *80*, 1127.
- (3) (a) Yoshino, Y.; Kurahashi, T.; Matsubara, S. *J. Am. Chem. Soc.* **2009**, *131*, 7494. (b) Kajita, Y.; Kurahashi, T.; Matsubara, S. *J. Am. Chem. Soc.* **2008**, *130*, 17226. (c) Miura, T.; Yamauchi, M.; Murakami, M. *Org. Lett.* **2008**, *10*, 3085. (d) Kajita, Y.; Matsubara, S.; Kurahashi, T. *J. Am. Chem. Soc.* **2008**, *130*, 6058.
- (4) For recent reviews of carbonylative annulations using CO as a carbonyl source, see: (a) Chatani, N. *Chem. Rev.* **2008**, *8*, 201. (b) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644. (c) Vasapollo, G.; Mele, G. *Curr. Org. Chem.* **2006**, *10*, 1397. (d) Vizer, S. A.; Yezhzhaynov, K. B.; Al Quntar, A. A.; Dembitsky, V. M. *Tetrahedron* **2004**, *60*, 5499.
- (5) For recent examples, see: (a) Krishnamoorthy, R.; Lam, S. Q.; Manley, C. M.; Herr, R. J. *J. Org. Chem.* **2010**, *75*, 1251. (b) Kochi, T.; Urano, S.; Seki, H.; Mizushima, E.; Sato, M.; Kakiuchi, F. *J. Am. Chem. Soc.* **2009**, *131*, 2792. (c) Yasui, Y.; Takemoto, Y. *Chem. Rev.* **2008**, *8*, 386, and references cited therein.
- (6) The 2-quinolone core is a ubiquitous subunit in many alkaloids with various biological activities, and 2-quinolones serve as valuable intermediates in organic synthesis. For examples, see: (a) Jayashree, B. S.; Thomas, S.; Nayak, Y. *Med. Chem. Res.* **2010**, *19*, 193. (b) Godard, A.; Fourquez, J. M.; Tamion, R.; Marsais, F.; Quéguiner, G. *Synlett* **1994**, 235.
- (7) Recently, the synthesis of 2-quinolones by intramolecular cyclization of carbamoyl chlorides bearing an alkene has been reported. See: Yasui, Y.; Kakinokihara, I.; Takeda, H.; Takemoto, Y. *Synthesis* **2009**, 3989.
- (8) For selected syntheses and functionalizations of 2-quinolones, see: (a) Tang, D.-J.; Tang, B.-X.; Li, J.-H. *J. Org. Chem.* **2009**, *74*, 6749. (b) Kobayashi, Y.; Harayama, T. *Org. Lett.* **2009**, *11*, 1603. (c) Tadd, A. C.; Matsuno, A.; Fielding, M. R.; Willis, M. C. *Org. Lett.* **2009**, *11*, 583. (d) Wang, Z.; Fan, R.; Wu, J. *Adv. Synth. Catal.* **2007**, *349*, 1943. (e) Vicente, J.; Abad, J.-A.; López-Serrano, J.; Jones, P. G.; Nájera, C.; Botella-Segura, L. *Organometallics* **2005**, *24*, 5044. (f) Kadnikov, D. V.; Larock, R. C. *J. Org. Chem.* **2004**, *69*, 6772. (g) Kadnikov, D. V.; Larock, R. C. *J. Organomet. Chem.* **2003**, *687*, 425.
- (9) (a) Iwai, T.; Fujihara, T.; Tsuji, Y. *Chem. Commun.* **2008**, 6215. (b) Fristrup, P.; Kreis, M.; Palmelund, A.; Norrby, P.-O.; Madsen, R. *J. Am. Chem. Soc.* **2008**, *130*, 5206.
- (10) Rh-catalyzed annulation of acid chlorides with internal alkynes to give indenones via migration/reinsertion of CO has been reported. See: Kokubo, K.; Matsumasa, K.; Miura, M.; Nomura, M. *J. Org. Chem.* **1996**, *61*, 6941.
- (11) (a) Iwai, T.; Fujihara, T.; Terao, J.; Tsuji, Y. *J. Am. Chem. Soc.* **2009**, *131*, 6668. (b) Fujihara, T.; Katafuchi, Y.; Iwai, T.; Terao, J.; Tsuji, Y. *J. Am. Chem. Soc.* **2010**, *132*, 2094.
- (12) See the Supporting Information for details.
- (13) Lemoucheux, L.; Rouden, J.; Ibazizene, M.; Sobrio, F.; Lasne, M.-C. *J. Org. Chem.* **2003**, *68*, 7289.
- (14) For oxidative addition of carbamoyl chlorides to palladium, see: Hiwatari, K.; Kayaki, Y.; Okita, K.; Ukai, T.; Shimizu, I.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 2237, and references cited therein.
- (15) For the synthesis and characterization of arylamide-iridacycle complexes from amines and CO, see: Rahim, M.; Bushweller, H.; Ahmed, K. J. *Organometallics* **1994**, *13*, 4952.

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