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

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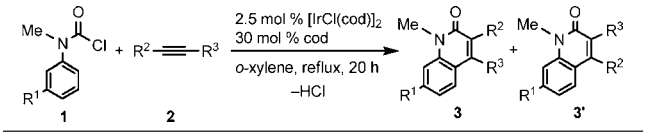
Abstract: An iridium complex successfully catalyzed the annulation of various *N*-arylcarbamoyl chlorides with internal alkynes to afford 2-quinolones in good to excellent yields. The present reaction is widely applicable to substrates with various functionalities. An amide−iridacycle complex was isolated, 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 PPh_3 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 Na_2CO_3 and N(*i*-Pr)$_2$Et 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 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**.

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-$MeOC_6H_4$, 4-$MeOC_6H_4$	**3bd**	89[e]	−
6	**1b**: MeO	**2e**: 4-ClC_6H_4, 4-ClC_6H_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**: $MeOCH_2$, *n*-C_5H_{11}	**3ah**	91	72/28
10	**1a**: H	**2i**: Me, 2-$MeOC_6H_4$	**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 %).

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

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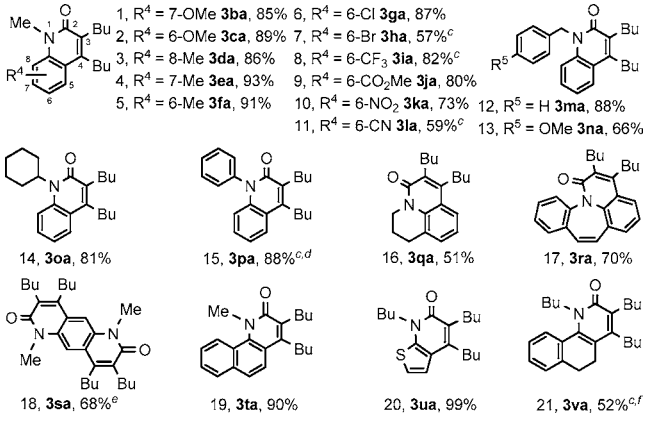
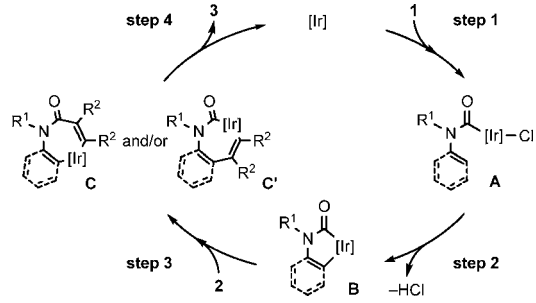
Table 2. Synthesis of **3** from **1** and **2a** (entry, product, yield)[a,b]

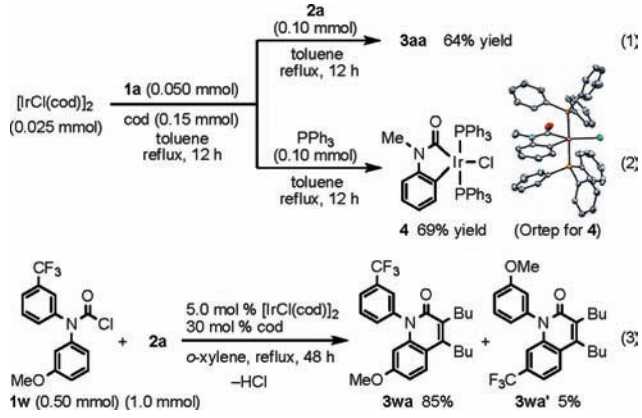


[a] Conditions: **1** (0.50 mmol), **2a** (1.0 mmol), $[IrCl(cod)]_2$ (0.0125 mmol, 2.5 mol %), and cod (0.15 mmol, 30 mol %) in refluxing *o*-xylene (1.0 mL) for 20 h. [b] Isolated yields. [c] $[IrCl(cod)]_2$ (0.025 mmol, 5.0 mol %). [d] For 36 h. [e] **1s** (0.25 mmol), **2a** (1.0 mmol), $[IrCl(cod)]_2$ (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**, PPh_3 (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 PPh_3 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*-arylcarbamoyl 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.

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