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Palladium-Catalyzed Cyclocarbonylation of *o*-Iodoanilines with Imidoyl Chlorides to Produce Quinazolin-4(*3H*)-ones

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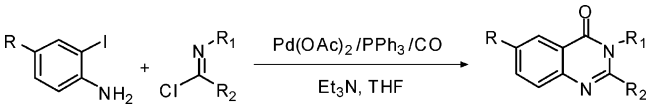
ABSTRACT



A wide variety of substituted quinazolin-4(*3H*)-ones were prepared in 63–91% yields by the palladium-catalyzed cyclocarbonylation of *o*-iodoanilines with imidoyl chlorides and carbon monoxide. The reaction is believed to proceed via in situ formation of an amidine, followed by oxidative addition, CO insertion, and intramolecular cyclization to give the substituted quinazolin-4(*3H*)-ones.

Quinazolin-4(*3H*)-ones are an important class of fused heterocyclic compounds known as the core structural skeleton in a variety of natural products and synthetic drugs.[1] They exhibit a wide range of biological activities such as anticancer,[2] antidiabetic,[3] antiinflammatory,[4] antimicrobial,[5] anticonvulsant,[6] antibacterial,[7] antimalarial,[8] antiallergy,[9] and analgesic[10] properties. There are a number of synthetic methods available for the preparation of quinazolin-4(*3H*)-ones.[11] The most common synthetic route involves the amidation of 2-aminobenzoic acid or its derivatives, i.e., 2-aminobenzonitrile, 2-aminobenzoate, and 2-arylnitrilium salts, followed by oxidative ring closure.[12,13] Other synthetic pathways include the cyclization of anthranilamides with aldehydes,[14] and with ketones or acid chlorides under acidic or basic conditions.[15] These traditional methods often suffer from low yields, multistep reactions, or harsh reaction conditions. Recently, several new synthetic methods were reported including solid-phase synthesis,[16] microwave irradiation,[17] and ionic liquid as a medium.[18] A few examples

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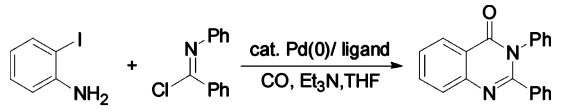
of transition metal-catalyzed routes to quinazolin-4(*3H*)-ones have appeared in the literature, including the use of $PdCl_2(PPh_3)_2$ and $SnCl_2$ catalysis.[19] Quinazolin-4(*3H*)-ones were also synthesized employing dicobalt octacarbonyl,[20] ruthenium or platinum complexes,[21] and titanium reagents[22] as catalysts. One of us has developed a palladium-catalyzed reaction of *o*-iodoanilines with heterocumulenes to afford quinazolin-4(*3H*)-ones derivatives.[23]

2-Substituted-4*H*-3,1-benzoxazin-4-ones derivatives were isolated from the Pd-catalyzed cyclocarbonylation of *o*-iodoanilines with acid chlorides and carbon monoxide.[24] Herein, we reported an effective palladium-catalyzed three-component reaction of *o*-iodoanilines, imidoyl chlorides, and carbon monoxide affording substituted quinazolin-4(*3H*)-ones bearing a variety of functional groups.

The reaction of *o*-iodoaniline **1a** with *N*-phenylbenzimidoyl chloride **2a** was chosen as a model system (Table 1).

Table 1. Optimization of the Reaction Conditions for the Reaction of *o*-Iodoaniline with *N*-(Phenyl)benzimidoyl Chloride[a]



1a **2a** **3a**

entry	catalyst system	time (h)	temp (°C)	CO (psi)	yield (%)[b]
1	$Pd(OAc)_2$/dppb	48	110	500	trace
2	$Pd(OAc)_2$/dppp	48	110	500	trace
3	$Pd(OAc)_2/PPh_3$	48	110	500	74
4	$Pd(OAc)_2$/x-phos	48	110	500	46
5	$Pd(PPh_3)_4$	48	110	500	72
6	$Pd_2(dba)_3/PPh_3$	48	110	500	63
7	$Pd_2(dba)_3$/x-phos	48	110	500	40
8	$Pd(OAc)_2/PPh_3$	24	110	500	48
9	$Pd(OAc)_2/PPh_3$	48	110	300	62
10	$Pd(OAc)_2/PPh_3$	48	80	500	54
11	$Pd(OAc)_2/PPh_3$	48	140	500	75

[a] Reaction conditions: *o*-iodoaniline **1a** (1.0 mmol), ***N***-(phenyl) benzimidoyl chloride **2a** (1.0 mmol), Pd cat. (0.03 mmol), PPh_3 or Xphos (0.135 mmol), or dppp or dppb, (0.07mmol), Et_3N (2.1 mmol), CO 300 or 500 psi, THF (10 mL). [b] Isolated yield.

Initially, treatment of **1a** (1.0 mmol) and **2a** (1.0 mmol) at 500 psi of carbon monoxide, in the presence of 0.03 mmol of $Pd(OAc)_2$ and 0.07 mmol of 1,4-bis(diphenylphosphino)-butane (dppb), or 1,4-bis (diphenylphosphino)propane (dppp) and 2.1 mmol of Et_3N in 10 mL of THF, at 110 °C for 48 h afforded trace amounts of 2,3-diphenyl-quinazoline-4(*3H*)-one (**3a)** (Table 1, entries 1 and 2). Performing the same reaction using 0.135 mmol of triphenylphosphine (PPh_3) instead of bidentate phosphine ligands resulted in the isolation of **3a** in 74% yield (Table 1, entry 3). When employing the bulky and electron-rich monophosphine Xphos (2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl), the yield of product **3a** was reduced to 46% (Table 1, entry 4). Thus, the choice of ligand is important for this transformation. The use of $Pd(PPh_3)_4$ instead of $Pd(OAc)_2$ combined with PPh_3 gave a similar result (Table 1, entry 5). $Pd_2(dba)_3$ (tris(dibenzylideneacetone)−dipalladium(0)−chloroform adduct) can be used for this reaction, but it is not as effective as $Pd(OAc)_2$ (Table 1, entries 6 and 7). We selected $Pd(OAc)_2$ and PPh_3 to use as the catalytic system for the reaction of a variety of imidoyl chlorides with *o*-iodoanilines and CO.

Other reaction parameters were also examined. Shorter reaction times, lower pressures of carbon monoxide, or lower temperatures, resulted in incomplete consumption of starting materials (Table 1, entries 8−10). A slight increase in the yield was observed by increasing the reaction temperature to 140 °C (Table 1, entry 11).

The scope of the reaction was explored by treating a variety of imidoyl chlorides with *o*-iodoanilines under the optimized reaction conditions. The results are summarized in Table 2.

Reaction of **1a** with an imidoyl chloride containing 4-methoxyphenyl (**2b**) or 4-methylphenyl (**2c**−**e**) substituents gave 2,3-disubstituted quinazolin-4(*3H*)-ones **3b**−**e** in 70−91% yields (Table 2, entries 2−5), while the use of imidoyl chlorides having a 4-chlorophenyl group afforded the products **3f** and **3g** in 67% and 65% yields, respectively (Table 2, entries 6 and 7). The reaction occurs more slowly when an imidoyl chloride containing two 4-chlorophenyl groups was used as the reactant with **3h** formed in 63% yield after 72 h (Table 2, entry 8). An electron-donating group increases the reactivity of the imidoyl chloride to give a better product yield. Treatment of **1a** with imidoyl chlorides bearing alkyl groups also afforded the expected products **3i**−**k** in 81−90% yields (Table 2, entries 9−11). The molecular structure of **3i** was confirmed by an X-ray crystallographic determination (Figure 1).

The annulation method could be extended to an imidoyl chloride bearing a furan substituent. It was noteworthy that, under the standard conditions, the expected quinazoline-4(*3H*)-one **3l** was obtained in 13% yield, while amidine **4** was isolated as a major product in 55% yield (Scheme 1). The structure of compound **4** was confirmed by X-ray diffraction (Figure 2). A beneficial effect of increasing the reaction temperature on the reaction was observed. The yield of **3l** increased to 87% when the temperature was raised to

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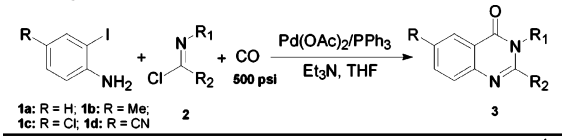
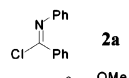
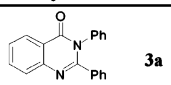
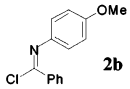
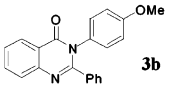
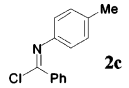
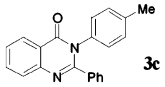
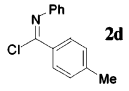
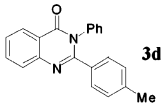
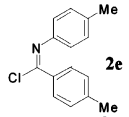
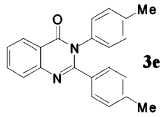
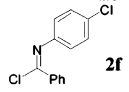
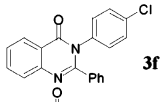
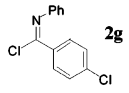
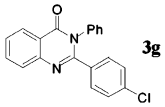
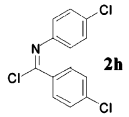
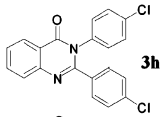
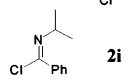
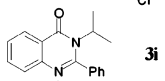
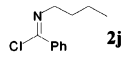
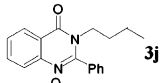
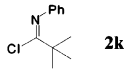
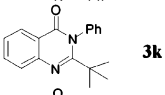
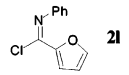
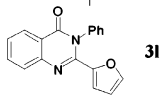
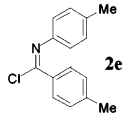
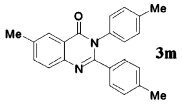
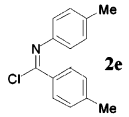
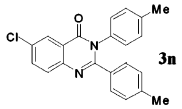
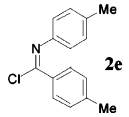
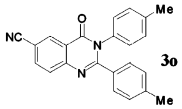
Table 2. Synthesis of Quinazolin-4(*3H*)-ones via Palladium-Catalyzed Cyclocarbonylation of *o*-Iodoanilines **1** with Imidoyl Chlorides **2**[a]



entry	1	2	product 3	yield(%)[b]
1	1a	 2a	 3a	74
2	1a	 2b	 3b	80
3	1a	 2c	 3c	76
4	1a	 2d	 3d	70
5	1a	 2e	 3e	91
6	1a	 2f	 3f	67
7	1a	 2g	 3g	65
8	1a	 2h	 3h	63[c]
9	1a	 2i	 3i	82
10	1a	 2j	 3j	81
11	1a	 2k	 3k	90
12	1a	 2l	 3l	87[d]
13	1b	 2e	 3m	66
14	1c	 2e	 3n	74
15	1d	 2e	 3o	67

[a] *o*-Iodoaniline **1** (1.0 mmol), imidoyl chloride **2** (1.0 mmol), $Pd(OAc)_2$ (0.03 mmol), PPh_3(0.135 mmol), Et_3N (2.1 mmol), CO 500 psi, THF (10 mL), 110 °C, 48 h. [b] Isolated yield. [c] 72 h. [d] 150 °C.

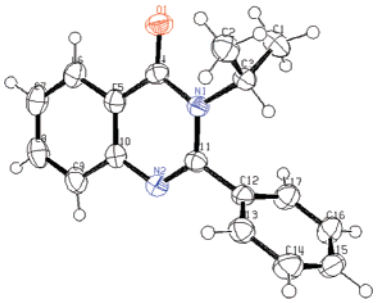
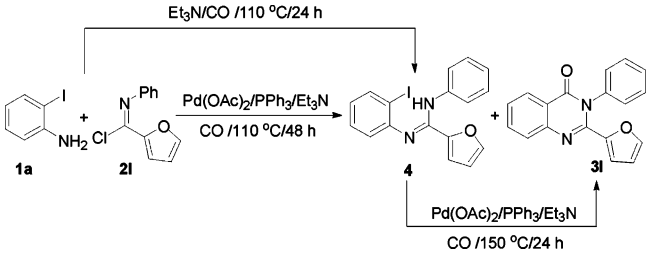


Figure 1. Perspective view of compound **3i**.

150 °C (Table 2, entry 12). A more extensive investigation of the reaction showed that amidine **4** could be obtained nearly quantitatively, in the presence of Et_3N without a Pd catalyst. Further treatment of the amidine **4** could give **3l** in good yield using the $Pd(OAc)_2/PPh_3$ catalytic system at 150 °C (Scheme 1). This result suggests that the cyclocarbonylation reaction may proceed via formation of amidine **4**.

Scheme 1



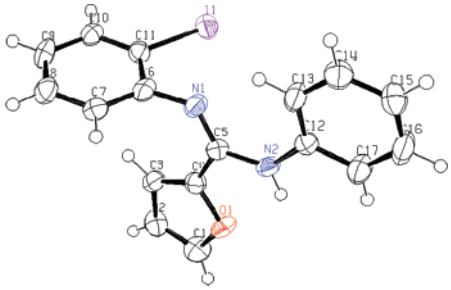
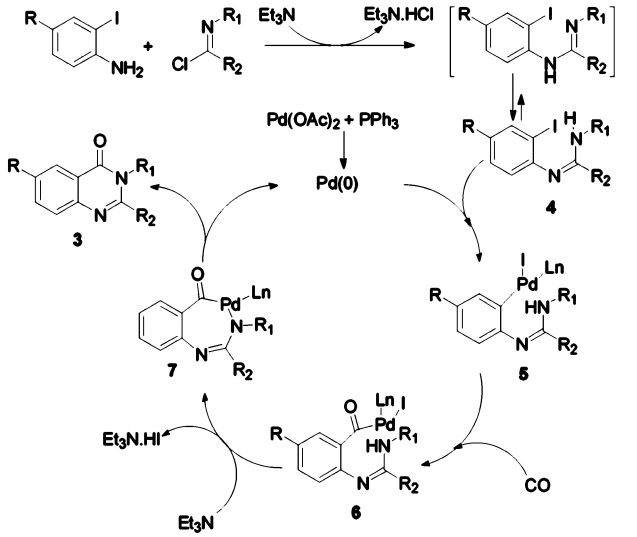


Figure 2. Perspective view of compound **4**.

The palladium-catalyzed carbonylation reaction was also successfully extended to *o*-iodoanilines possessing various substituents to afford 2,3,6-trisubstitued quinazolin-4(*3H*)-ones in 66−74% yields (Table 2, entries 13−15).

A possible reaction mechanism for the formation of quinazolin-4(*3H*)-ones **3** is outlined in Scheme 2. Reaction of the imidoyl chloride with the amino group of the

Scheme 2. Proposed Reaction Mechanism



o-iodoaniline in the presence of base, following a process of NH tautomerism, could give the amidine intermediate **4**. Oxidative addition of **4** to the in situ generated palladium(0) species[25] leads to a palladium complex **5**. Carbon monoxide insertion into the aryl carbon−palladium bond of **5** affords the aroylpalladium iodide complex **6**. Base-catalyzed intramolecular cyclization of **6** gives a palladacycle **7** which undergoes reductive elimination affording quinazolin-4(*3H*)-one **3** with regeneration of palladium(0).

In conclusion, we have demonstrated an effective approach for the one-step synthesis of quinazolin-4-(*3H*)-ones from readily available imidoyl chlorides and *o*-iodoanilines by a palladium-catalyzed three-component process. The method tolerates a range of functional groups, and substituted quinazoline-4(*3H*)-ones were formed in 63−91% yields.

Acknowledgment. We are grateful to the Natural Sciences and Engineering Research Council of Canada (NSERC) for support of this research.

Supporting Information Available: Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra and the crystal structure analysis of **3i** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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