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Tandem Palladium-Catalyzed Addition/Cyclocarbonylation: An Efficient Synthesis of 2-Heteroquinazolin-4(*3H*)-ones

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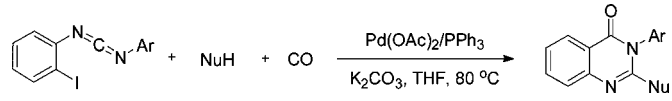
ABSTRACT



A highly practical and efficient method for the synthesis of 2-heteroquinazolin-4(*3H*)-ones has been developed by a palladium-catalyzed tandem reaction. Under mild reaction conditions (80 °C, 100 psi), a wide variety of 2-heteroquinazolin-4(3*H*)-ones were obtained in good to excellent yields.

2-Heteroquinazolin-4(3*H*)-ones have recently attracted considerable attention due to their diverse biological and pharmacological activities.[1] For example, 2-aminoquinazolin-4(3*H*)-one derivatives have shown high activities as dopamine agonists,[2] histamine H_4 receptor inverse agonists,[3] anti-inflammatory,[4] antitumor,[5] antihypertentive,[6] anticonvulsant,[7] antihyperglycemic,[8] and antibacterial[9] agents.

A number of synthetic methods for the preparation of 2-heteroquinazolin-4(*3H*)-ones have been developed. In general, the synthetic methods to such compounds can be classified into the following five categories: (1) alkylation of 2,4-quinazolinediones[10] or 2-thioxoquinazolin-4-ones;[11] (2) the direct substitution of 2-chloroquinazolin-4(3*H*)-ones[12] or its analogues such as 2-alkylthioquinazolin-4(3*H*)-ones,[13] 2-cyanoquinazolin-4(3*H*)-ones[14] by nucleophiles; (3) amidation of 2-aminobenzoic acid[15] and its

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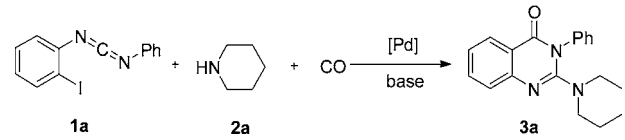
derivatives, i.e., 2-aminobenzonitrile,[16] 2-aminobenzoate,[17] and isatoic anhydride;[18] (4) reaction of nucleophiles, i.e., guanidines, with *o*-fluorobenzoyl derivatives;[19] (5) the tandem aza-Witting reaction of iminophosphorane.[20]

These procedures often suffer from certain drawbacks such as multistep reactions, harsh reaction conditions, and low yields. Recently, several new synthetic methods have been reported including copper-catalyzed amination of 2-halobenzyl acids,[21] solid-supported synthesis,[22] microwave irradiation,[23] and synthesis from aromatic amines through Friedel−Crafts reaction.[24] We have been interested in the one-step synthesis of carbonyl-containing heterocycles by carbonylation reactions, which provide convenient and efficient approaches to potentially useful carbonyl-containing heterocyclic compounds.[25] One of us reported that the palladium-catalyzed cyclocarbonylation of *o*-iodoanilines with heterocumulenes afforded quinazolin-4(3*H*)-ones.[26] Herein, we report a novel and efficient protocol to synthesize various 2-heteroquinazolin-4(3*H*)-ones under mild conditions.

Initially, the reaction of *N*-(2-iodophenyl)-*N*′-phenylcarbodiimide (**1a**)[27] with piperidine (**2a**) was chosen as the model reaction to optimize the reaction conditions which included the catalyst, solvent, and base under carbon monoxide pressure (Table 1). Using $Pd_2(dba)_3$·$CHCl_3$−PPh_3−Cs_2CO_3 as the catalytic system, the desired product **3a** was obtained in 92% yield (entry 1). Lower product yields were obtained when Et_3N (86%) or K_2CO_3 (88%) was used instead of Cs_2CO_3 (entries 2 and 3). However, using the $Pd(OAc)_2$−K_2CO_3 catalytic system under the same reaction conditions gave **3a** in 93% isolated yield (entry 4). The reaction system was not sensitive to the solvent and the pressure of carbon monoxide (entries 4 and 6−9). Even at 100 psi of CO, the desired product **3a** was isolated in 93% yield (entry 9). The product yields decreased slightly as the amount of palladium was reduced (entries 9−11). On the basis of the results, the $Pd(OAc)_2$ (4%)−K_2CO_3−CO (100 psi) catalytic system was chosen as the optimal reaction conditions (entry 9). It should be noted that using 2.0 equiv of piperidine as the nucleophile afforded no byproducts (entry 12), which indicated that the intramolecular carbonylation is very regioselective to form quinazolin-4(3*H*)-one (**3a**).

Using the optimized reaction conditions, the scope of this reaction was extended to a variety of carbodiimides and nucleophiles, and the results are summarized in Table 2. The reaction of *N*-(2-iodophenyl)-*N*′-phenyldicarbodiimide (**1a**) with piperidine (**2a**), 2-methylpiperidine (**2b**), and 2,6-dimethylpiperidine (**2c**) gave the products in 93%, 94%, and 92% yields, respectively, indicating that the methyl group which is closest to the nitrogen atom has no major effect on the reaction (entries 1−3).

Table 1. Optimization of the Reaction Conditions for the Reaction of *N*-(2-Iodophenyl)-*N*′-phenylcarbodiimide with Piperidine[a]



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

entry	[Pd]	base	P_{CO} (psi)	solvent	yield[b] (%)
1	$Pd_2(dba)_3$	Cs_2CO_3	500	THF	92
2	$Pd_2(dba)_3$	Et_3N	500	THF	85
3	$Pd_2(dba)_3$	K_2CO_3	500	THF	88
4	$Pd(OAc)_2$	K_2CO_3	500	THF	93
5	$PdCl_2$	K_2CO_3	500	THF	86
6	$Pd(OAc)_2$	K_2CO_3	500	PhMe	92
7	$Pd(OAc)_2$	K_2CO_3	300	PhMe	91
8	$Pd(OAc)_2$	K_2CO_3	100	PhMe	87
9	$Pd(OAc)_2$	K_2CO_3	100	THF	93
10	$Pd(OAc)_2$	K_2CO_3	100	THF	90[c]
11	$Pd(OAc)_2$	K_2CO_3	100	THF	86[d]
12	$Pd(OAc)_2$	K_2CO_3	100	THF	92[e]

[a] All reactions were carried out using 0.5 mmol of **1a**, 0.55 mmol of **2a**, [Pd]/PPh_3/**1a** = 4:8:100, 2.0 equiv of base, 6 mL of solvent, 80 °C, 15 h. [b] Isolated yield. [c] [Pd]/PPh_3/**1a** = 3:6:100. [d] [Pd]/PPh_3/**1a** = 2:4:100. [e] 1. 0 mmol of **2a**.

In a similar fashion, reaction of carbodiimide (**1a**) with diethylamine (**2h**) and diisopropylamine (**2i**) afforded the corresponding quinazolin-4(3*H*)-ones in 93% and 91% yields, respectively (entries 11 and 15). Using *N*-methylaniline instead of aliphatic amines as the *N*-nucleophile, the analogous product (**3p**) was obtained in 55% yield. The electronic effect of the substituents on the aromatic rings of carbodiimides (**1**) was also investigated. This cyclization process tolerates both electron-donating (*p*-MeO) and electron-withdrawing (*p*-Cl) groups on the aromatic rings of carbodiimides (entries 6−9 and 11−14).

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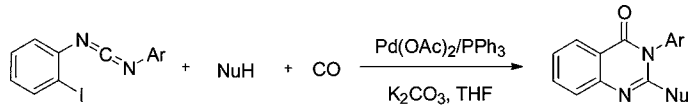
(27) The carbodiimdes **1a**−**d** were efficiently prepared by the known metathesis reactions of corresponding isocyanates with *N*-(2-iodophenyl)-triphenyliminophosphorane, and the latter was synthesized in 98% yield by the reaction of 2-iodoaniline with PPh_3 in precence of Et_3N and C_2Cl_6.

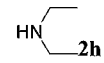
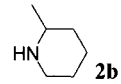
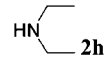
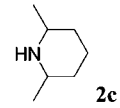
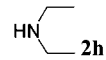
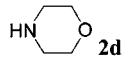
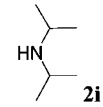
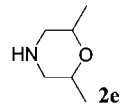
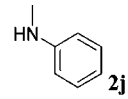
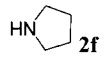
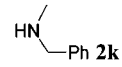
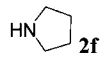
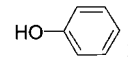
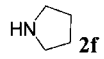
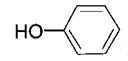
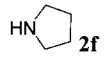
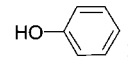
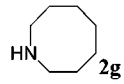
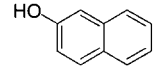
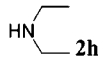
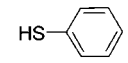
Table 2. One-Step Synthesis of 2-Heteroquinozalin-4(3*H*)-ones[a]



1a Ar = Ph
1b Ar = 4-MeOC$_6$H$_4$
1c Ar = 4-ClC$_6$H$_4$
1d Ar = 1-Naph

2

3

entry	1	NuH	product	yield (%)[b]	entry	1	NuH	product	yield (%)[b]
1	**1a**	 **2a**	**3a**	93	12	**1b**	 **2h**	**3l**	93
2	**1a**	 **2b**	**3b**	94	13	**1c**	 **2h**	**3m**	91
3	**1a**	 **2c**	**3c**	92	14	**1d**	 **2h**	**3n**	70
4	**1a**	 **2d**	**3d**	88	15	**1a**	 **2i**	**3o**	91
5	**1a**	 **2e**	**3e**	72	16	**1a**	 **2j**	**3p**	55
6	**1a**	 **2f**	**3f**	96	17	**1a**	 Ph **2k**	**3q**	95
7	**1b**	 **2f**	**3g**	93	18	**1a**	 **2m**	**3r**	73
8	**1c**	 **2f**	**3h**	92	19	**1b**	 **2m**	**3s**	64
9	**1d**	 **2f**	**3i**	70	20	**1d**	 **2m**	**3t**	50
10	**1a**	 **2g**	**3j**	94	21	**1a**	 **2n**	**3u**	66
11	**1a**	 **2h**	**3k**	93	22	**1a**	 **2o**	**3v**	0

[a] All reactions were carried out using 0.5 mmol of **1**, 0.55 mmol of **2**, [Pd]/PPh$_3$/**1** = 4:8:100, 2.0 equiv of base, 6 mL of solvent, under 100 psi of CO, 80 °C, for 15 h. [b] Isolated yield.

The yields of products **3i** and **3n** decreased slightly due to the 1-naphthyl group on the nitrogen atom of the carbodiimide (**1d**), which affects steric hindrance in the first-step addition reaction. When phenol and 2-naphthol were used as nucleophiles, the desired products were formed in reasonable yields (entries 18−21). When thiophenol was used as the nucleophile, product (**3v**) was not formed. A possible reason why **3v** was not formed is because the palladium active species is blocked by the in situ fromed intermediate. For the same reason, reaction of carbodiimide **1a** with pyrazole did not afford the corresponding product.

The cyclocarbonylation reaction appears to proceed through in situ generation of isomeric guanidines (**4a** and **4b**, Scheme 1) from an intermolecular addition of the nucleophile (**2**) to *o*-iodoarylcarbodiimides (**1**). Oxidative addition of the intermediate **4** to the in situ generated palladium(0) species[28] leads to complex **5**, which is followed by the formation of aroylpalladium iodide complex **6** via carbon monoxide insertion into the aryl carbon−palladium bond of **5**. Thus, base-catalyzed intramolecular cyclization of **6** gives a palladacycle **7**,

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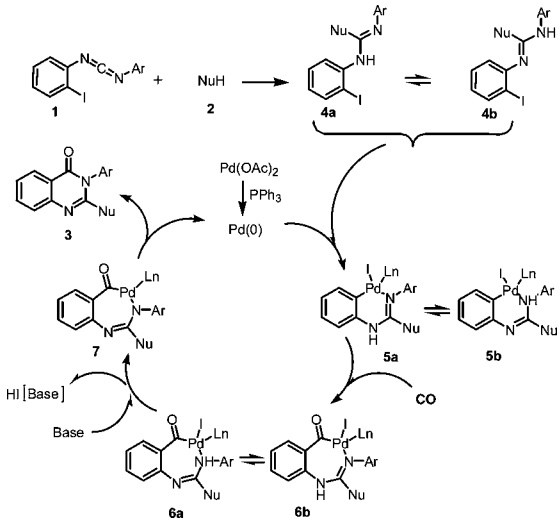
Scheme 1. Possible Reaction Mechanism



which undergoes reductive elimination affording the quinazolin-4(3*H*)-one **3** with regeneration of the palladium(0) species.

In summary, we have demonstrated a simple and efficient strategy for the one-step synthesis of potentially important 2-heteroquinazolin-4(3*H*)-one derivatives by palladium-catalyzed intermolecular addition and intramolecular cyclocarbonylation cascade reaction protocol. A large number of 2-aminoquinazolin-4(3*H*)-ones and 2-phenoxyquinazolin-4(3*H*)-ones were obtained in good to excellent yields.

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Supporting Information Available: Experimental procedures, spectroscopic data, and copies of ^{1}H and ^{13}C NMR spectra for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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