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One-Step Synthesis of Quinazolino[3,2-*a*]quinazolinones via Palladium-Catalyzed Domino Addition/Carboxamidation Reactions

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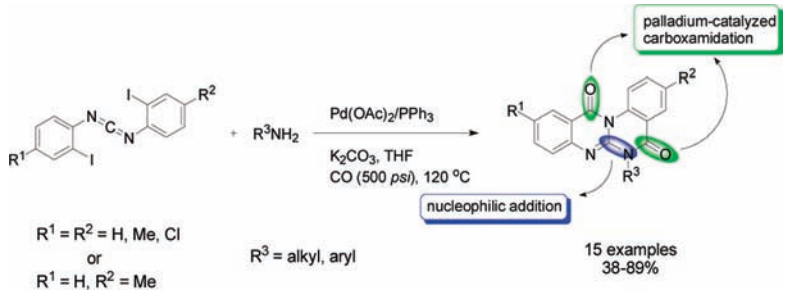
ABSTRACT



A highly efficient palladium-catalyzed domino process has been developed for the synthesis of quinazolino[3,2-*a*]quinazolinones by forming five new bonds in a single step. Despite the high density and variety of functional groups on the substrates, the tetracyclic quinazolinones were obtained in good to excellent yields.

Domino reactions have recently attracted considerable attention due to their high efficiency for the construction of complex molecular architectures from readily available building blocks.[1,2] These reactions typically entail the consecutive formation of multiple new bonds in a single step under identical reaction conditions, which potentially minimize requisite reagents, separation processes, waste, energy, time, and cost. Hence, the need to develop new efficient domino processes is of major interest to the synthetic community.

Ring-fused quinazolinones represent an important class of heterocyclic motifs that were found as the core structural skeletons in a variety of natural products such as rutaecarpine isolated from *Evodia rutaecarpa*,[3] luotonin A isolated from *Peganum nigellastrum*,[4] tryptanthrin isolated from *Couropita guianensis*[5] and deoxyvasicinone isolated from *Adhatoda vasica*.[6] In addition, these quinazolinone alkaloids exhibit a

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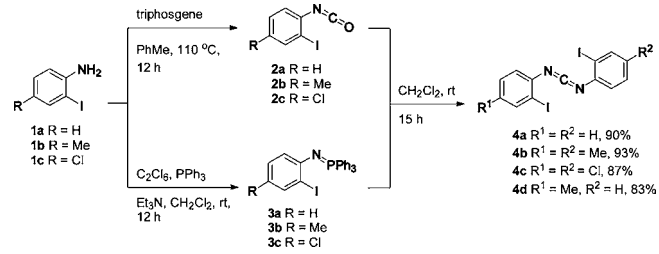
wide range of biological and medicinal activities, i.e., antimicrobial, anti-inflammatory, antidepressant, antirheumatic, and anti-infective properties.[7] There are a number of methods that have been developed for the synthesis of ring-fused quinazolinones;[7,8] however, these approaches often suffer from the poor availability of the requisite *o*-aminobenzoic acid derivatives, multistep reactions, and low yields. Recently several new synthetic strategies have been described including radical cascade reactions,[9] α-functionalization reactions of cyclic amines,[10] solid-supported synthesis,[11] and microwave irradiation.[12]

Transition-metal-catalyzed carbonylation reactions, particularly palladium-catalyzed carbonylations, are unique, powerful, and versatile tools for the synthesis of carbonyl-containing heterocyclic compounds.[13] We have described new protocols for the synthesis of ring-fused isoquinolinones,[14] lactones,[15] 1,3-benzothiazin-2-ones,[16] quinazolin-4(3*H*)-ones,[17] different ring-sized lactams,[18] 1,4-benzo or pyrido-oxazepinones,[19] and 2-acetyl-3,4-dihydronaphthalenones.[20] Herein, we report a highly novel and efficient domino strategy to synthesize 6-substituted quinazolino[3,2-*a*]quinazolinones.

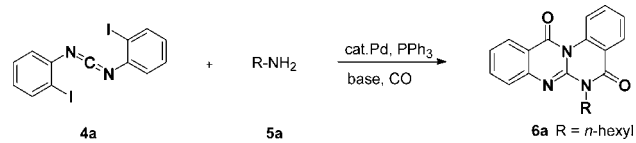
The starting materials, carbodiimides (**4a**−**d**), were efficiently prepared in 83−93% yields by metathesis reactions of the corresponding isocyanates (**2**) with *N*-(*o*-iodoaryl) triphenyliminophosphoranes (**3**) (Scheme 1).

Scheme 1. Synthesis of Carbodiimides **4a**−**d**



We began our investigation with *N*,*N*′-di-*o*-iodophenyl carbodiimide (**4a**) and hexylamine as the model substrates to examine the reaction conditions, which we previously developed for the synthesis of 2-heteroquinazolin-4(3*H*)-ones from the carbodiimides (Table 1) [4 mol % $Pd(OAc)_2$, 8 mol % PPh_3, K_2CO_3, 500 psi of CO, in THF].[17a] We were gratified to find that the desired 6-hexyl-12*H*-quinazolino-[3,2-*a*]quinazoline-5(6*H*),12-dione (**6a**) was obtained in 75% isolated yield. Performing the same reaction at 120 °C resulted in the isolation of **6a** in 81% yield (entry 2). Other reaction parameters, i.e., solvents and palladium catalyst, were investigated (entries 3−5), but no significant reactivity differences were observed. Hence, the simple system, $Pd(OAc)_2$ (4%)−PPh_3 (8%)−K_2CO_3, was chosen as the optimized catalytic system. It is noteworthy that using 2.0 equiv of hexylamine as the nucleophile afforded no byproducts (entry 6), demonstrating that the intramolecular carboxamidation is very regioselective to form the tetracyclic quinazolinone (**6a**).

Table 1. Optimization of the Reaction Conditions Using *N*,*N*′-Di-*o*-iodophenyl Carbodiimide with Hexylamine[a]



4a **5a** **6a** R = *n*-hexyl

entry	[Pd]	solvent	*t* (°C)	yield (%)[b]
1	$Pd(OAc)_2$	THF	80	75
2	$Pd(OAc)_2$	THF	120	81
3	$Pd_2(dba)_3$·$CHCl_3$	THF	120	81
4	$Pd(OAc)_2$	CH_2Cl_2	120	78
5	$Pd(OAc)_2$	PhMe	120	79
6	$Pd(OAc)_2$	THF	120	80[c]

[a] All reactions were carried out using 0.50 mmol of **4a**, 0.55 mmol of **5a**, [Pd]/PPh_3/**4a** = 4:8:100, 3.0 equiv of base, 6 mL of solvent, 500 psi of CO, 15 h. [b] Isolated yield. [c] 1.0 mmol of **5a**.

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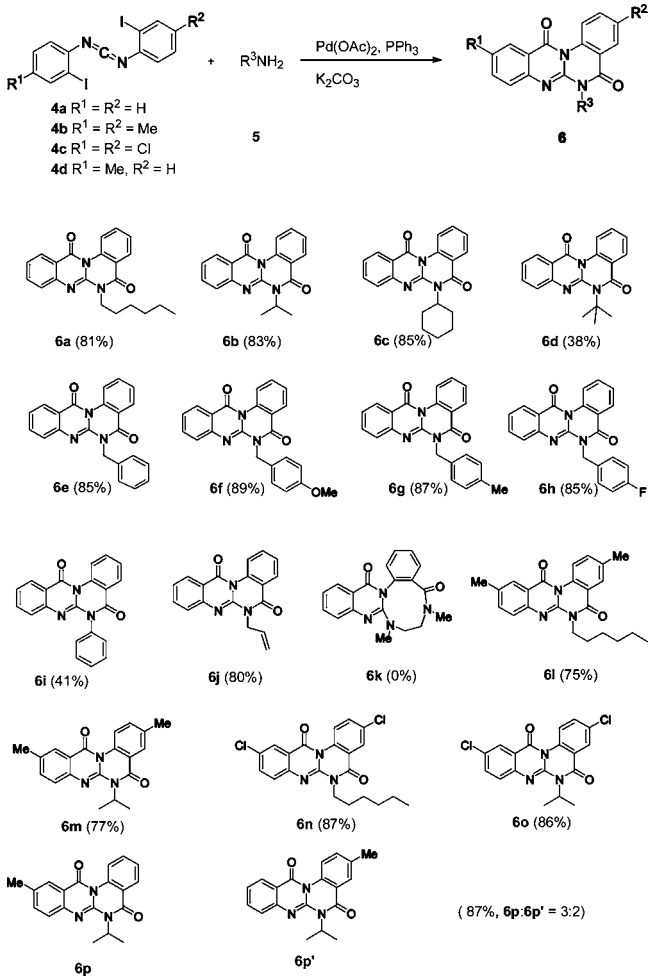
Scheme 2. Domino Synthesis of Tetracyclic Quinazolinones (**6**)[a,b]



[a] All reactions were carried out with 0.50 mmol of **4**, 0.55 mmol of **5**, $Pd(OAc)_2/PPh_3$/**4** = 4:8:100, 3.0 equiv of K_2CO_3, 6 mL of THF, 120 °C, 15 h. [b] Isolated yield.

The scope of this new protocol was further explored by reacting various carbodiimides (**4a**−**d**) with a wide variety of amines, and the results are summarized in Scheme 2.

The reaction of *N*,*N*′-di-*o*-iodophenyl carbodiimide (**4a**) with hexylamine, isopropylamine, and cyclohexylamine afforded target products in excellent isolated yields (81−85%), revealing that the methyl or methylene group that is closest to the nitrogen atom does not influence the reaction (Scheme 2, products **6a**, **6b**, and **6c**). However, when *tert*-butylamine was employed as the nucleophile, the desired product (**6d**) was formed in low yields (10% yield at 80 °C and 38% yield at 120 °C), and this may be due to the strong steric hindrance effect of the *tert*-butyl group. Using benzylamine derivatives, including 4-hydrogen, 4-methyl, 4-methoxyl, and 4-fluorobenzylamine, as the nucleophiles gave the corresponding products in 85−89% yields (Scheme 2, products **6e**−**h**). Thus the reaction occurs independent of the electronic nature of the substituents on the benzyl group. In contrast, when aniline was used instead of an aliphatic amine, the reaction proceeded sluggishly, giving the analogous product (**6i**) in 41% yield. Surprisingly, the reaction of carbodiimide (**4a**) with *N*,*N*′-dimethylethylenediamine did not afford the desired medium-ring product (**6k**). The influence of the substituents on the aryl groups of carbodiimides (**4a**−**d**) was also examined (Scheme 2, products **6l**−**p**). These results suggest that the cascade process tolerates both electron-donating (*p*-MeO) and electron-withdrawing (*p*-Cl) groups on the aryl groups of carbodiimides. The same transformation of the unsymmetrical carbodiimide (**4d**) gave a mixture of the two products **6p**/**6p**′ in a 3/2 ratio, the latter ratio determined by ^{1}H NMR spectroscopic analysis of the mixture of **6p** and **6p**′.

In summary, we have demonstrated a highly novel and efficient method for the synthesis of 6-substituted quinazolino[3,2-*a*]quinazolinones via a palladium-catalyzed domino addition/carboxamidation reaction by forming five new bonds in one step. This protocol displays good functional group compatibility and provides a more facile and straightforward access to potentially important aza-fused tetracyclic quinazoline derivatives.

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

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