



Ligand-free palladium assisted insertion of isocyanides to urea derivatives for cascade synthesis of phenylamino-substituted quinazolinones



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ABSTRACT

Palladium catalyzed cascade coupling of substituted urea derivatives and *tert*-butyl isocyanide for the efficient synthesis of phenylamino-substituted quinazolinones has been developed in moderate to good yields. This method provides a short and alternative approach for the synthesis of quinazolinones derivatives which are valuable compounds with biological and pharmacological potentials. A plausible mechanistic scheme is proposed.

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Quinazolinones are among the most privileged scaffolds found in synthetic and natural products of biological and pharmacological importance.^{1,2} Therefore, the development of efficient synthetic methods to prepare new types of quinazolinone molecules for screening in medicinal and pharmaceutical programmes is continuously gaining enormous interest in both academia and industry. In particular, fused quinazolinones are widely found in several biologically active natural products such as, 2-methyl-4(3*H*)-quinazolinone,³ bouchardatine,⁴ luotonin (A, B, E),⁵ auranthine,⁶ circumdatin (C, F),⁷ and sclerotigenin.⁸

In recent years plethora of methods have been developed for the synthesis of substituted 2-phenyl quinazolinone derivatives (I) catalyzed by metal catalysts.⁹ Whereas only handful of approaches are available for the synthesis of 2-(phenylamino)quinazolin-4(3*H*)-ones derivatives (II), that also suffer from low yields and/or poorly accessible precursors and most importantly require several steps to achieve the final product (Fig. 1).¹⁰ In view of their broad range of biological activities and high pharmacological potential a concise method involving commercially available and cheap starting materials is still required for their practical synthesis. Recently, palladium assisted isocyanide insertion has become an attractive and efficient approach because of its intriguing selectivity and atom-economy toward the C–C and C–N bond formations.¹¹ In our ongoing efforts to develop new strategies for the diversity oriented

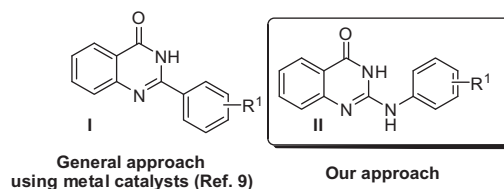


Figure 1. Structural comparison of substituted 2-phenyl quinazolinone and phenylamino-substituted quinazolinones.

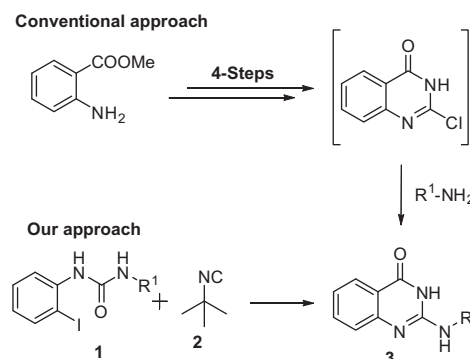
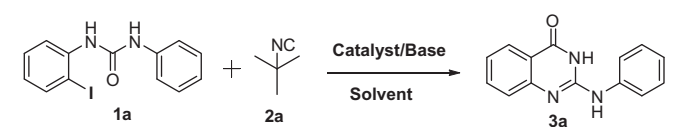


Figure 2. Cascade approach for the synthesis of phenylamino-substituted quinazolinones.

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Table 1
Optimization of reaction condition for the formation of phenylamino-substituted quinazolinones^a



Entry	Catalyst	Solvent	Base	Yield ^b
1	—	DMF	Cs ₂ CO ₃	0
2	Pd(PPh ₃) ₄	DMF	Cs ₂ CO ₃	36
3	PdCl ₂ (PPh ₃) ₂	DMF	Cs ₂ CO ₃	25
4	Pd ₂ (dba) ₃	DMF	Cs ₂ CO ₃	21
5	PdCl ₂	DMF	Cs ₂ CO ₃	13
6	Pd(OAc) ₂	DMF	Cs ₂ CO ₃	71
7	Pd(OAc) ₂	DMF	K ₂ CO ₃	31
8	Pd(OAc) ₂	DMF	K ₃ PO ₄	36
9	Pd(OAc) ₂	DMF	KOtBu	29
10	Pd(OAc) ₂	DMSO	Cs ₂ CO ₃	56
11	Pd(OAc) ₂	Dioxane	Cs ₂ CO ₃	43
12	Pd(OAc) ₂	Toluene	Cs ₂ CO ₃	28
13 ^c	Pd(OAc) ₂	DMF	Cs ₂ CO ₃	46

^a Reaction conditions: urea **1a** (1.0 mmol), *tert*-butyl isocyanide (1.2 mmol) (**2**), [Pd] catalyst (10 mol %), and base (2.0 mmol) in solvent (5 mL) under N₂ for 12 h at 120° C.

^b Isolated yield.

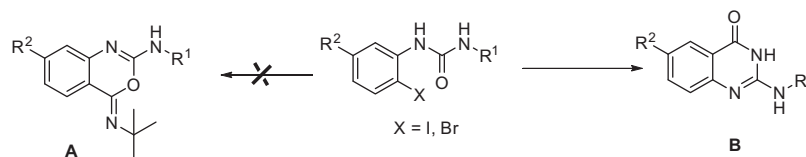
^c Catalyst loading was 5 mol %.

synthesis of bioactive heterocycles, and enlightened by the recent advancement, we have developed an isocyanide insertion reaction between substituted urea derivatives and *tert*-butyl isocyanide for

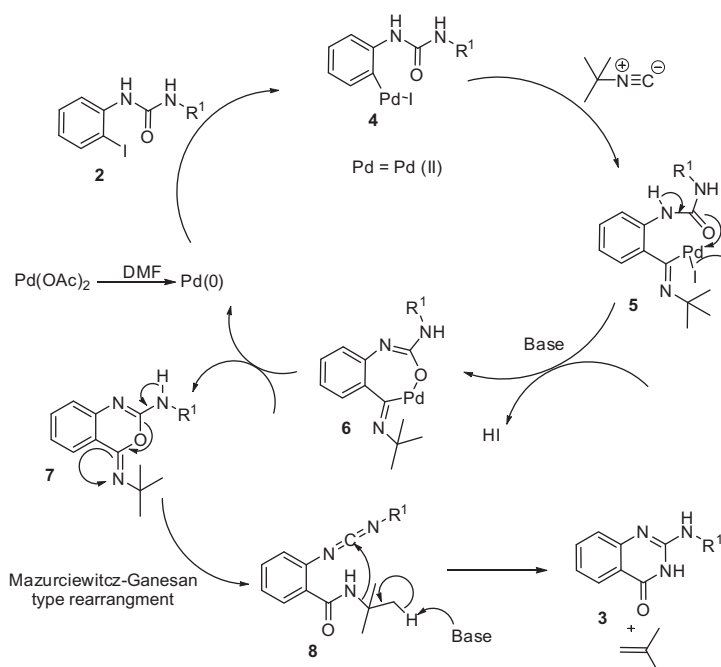
the synthesis of phenylamino-substituted quinazolinones derivatives.¹² Interestingly, the synthesis of these molecules traditionally require 4–5 steps in contrast to our highly concise and cascade process (Fig. 2).^{10b}

To prove our working hypothesis, urea derivative (**1a**) and *tert*-butyl isocyanide (**2**) were chosen as the model substrates to optimize the reaction conditions (Table 1). Subsequently, the effect of bases and solvents was further investigated using Pd(OAc)₂ as a catalyst. No product was formed when only Cs₂CO₃ was used to catalyze the isocyanide insertion reaction (Table 1, entry 1). A variety of palladium catalysts such as, Pd(PPh₃)₄ (Table 1, entry 2), PdCl₂(PPh₃)₂ (Table 1, entry 3), Pd₂(dba)₃ (Table 1, entry 4), and PdCl₂ (Table 1, entry 5) can effect this transformation to some extent, but Pd(OAc)₂ was selected as optimal catalyst for further studies. Many bases such as Cs₂CO₃, K₂CO₃, K₃PO₄, and KOtBu were used for the optimization, however the best results were obtained with Cs₂CO₃ (Table 1, entry 6). DMF emerged as the most suitable solvent among all the tested solvents such as DMSO, dioxane, and toluene (Table 1, entries 10–12). Lowering of the yield from 71% to 46% was observed when catalyst loading was decreased from 10 mol % to 5 mol % (Table 1, entry 13). Pleasingly, this reaction was very simple, high yielding, and most importantly, preliminary result is all the more interesting as no further addition of any ligand was required.

As depicted in Scheme 1, there are two possible products **A** and **B** from reaction under Pd-catalyzed conditions. ¹H NMR, ¹³C NMR, and mass spectral data of compounds confirmed that the products have the general structure **B**. For the better insight of the reaction product **B**, a tentative mechanism has also been proposed, where the first step involves the oxidative insertion of Pd to the urea



Scheme 1. Possible structure and selectivity in isocyanide insertion reaction.



Scheme 2. Plausible reaction pathway for the synthesis of phenylamino-substituted quinazolinones.

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