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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.

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

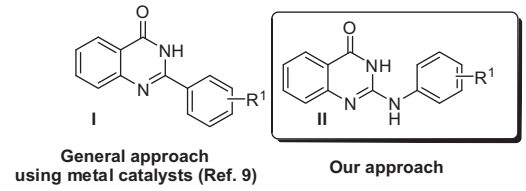

Figure 1. Structural comparison of substituted 2-phenyl quinazolinone and phenylamino-substituted quinazolinones.

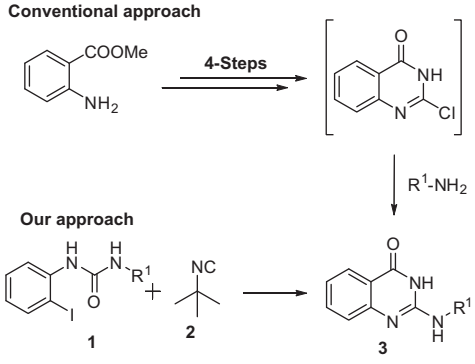

Figure 2. Cascade approach for the synthesis of phenylamino-substituted quinazolinones.

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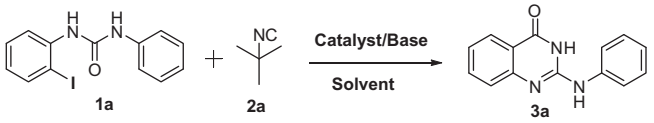
Table 1
Optimization of reaction condition for the formation of phenylamino-substituted quinazolinones[a]



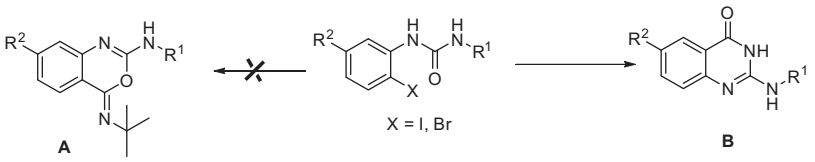
Entry	Catalyst	Solvent	Base	Yield[b]
1	—	DMF	Cs_2CO_3	0
2	$Pd(PPh_3)_4$	DMF	Cs_2CO_3	36
3	$PdCl_2(PPh_3)_2$	DMF	Cs_2CO_3	25
4	$Pd_2(dba)_3$	DMF	Cs_2CO_3	21
5	$PdCl_2$	DMF	Cs_2CO_3	13
6	$Pd(OAc)_2$	DMF	Cs_2CO_3	71
7	$Pd(OAc)_2$	DMF	K_2CO_3	31
8	$Pd(OAc)_2$	DMF	K_3PO_4	36
9	$Pd(OAc)_2$	DMF	KO*t*Bu	29
10	$Pd(OAc)_2$	DMSO	Cs_2CO_3	56
11	$Pd(OAc)_2$	Dioxane	Cs_2CO_3	43
12	$Pd(OAc)_2$	Toluene	Cs_2CO_3	28
13[c]	$Pd(OAc)_2$	DMF	Cs_2CO_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 N_2 for 12 h at 120° C.
[b] Isolated yield.
[c] Catalyst loading was 5 mol %.

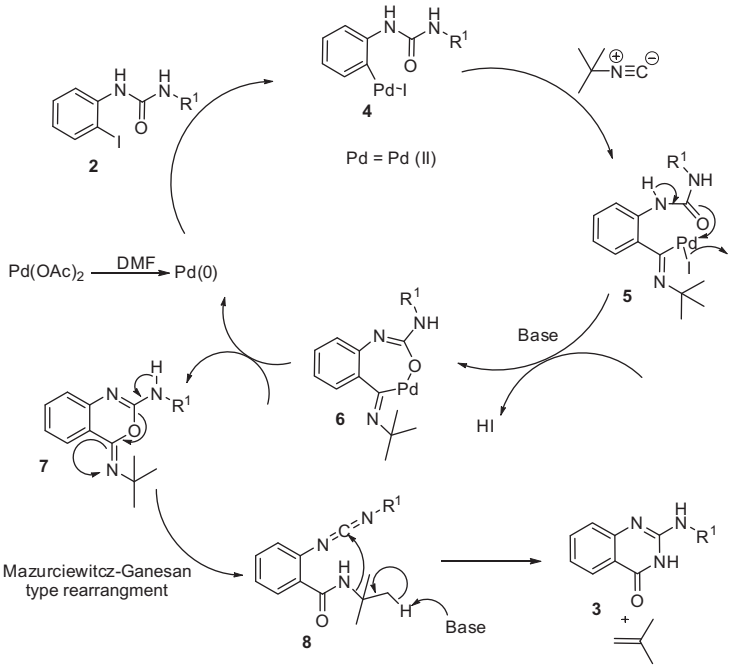
synthesis of bioactive heterocycles, and enlightened by the recent advancement, we have developed an isocyanide insertion reaction between substituted urea derivatives and *tert*-butyl isocyanide for the synthesis of phenylamino-substituted quinazolinones derivatives.[12] Interestingly, the synthesis 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 Cs_2CO_3 was used to catalyze the isocyanide insertion reaction (Table 1, entry 1). A variety of palladium catalysts such as, $Pd(PPh_3)_4$ (Table 1, entry 2), $PdCl_2(PPh_3)_2$ (Table 1, entry 3), $Pd_2(dba)_3$ (Table 1, entry 4), and $PdCl_2$ (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 Cs_2CO_3, K_2CO_3, K_3PO_4, and KO*t*Bu were used for the optimization, however the best results were obtained with Cs_2CO_3 (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. ^{1}H NMR, ^{13}C 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

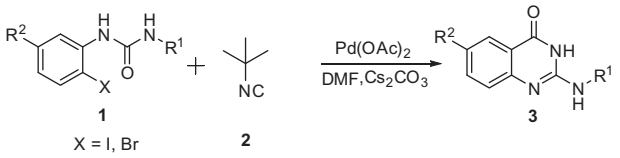


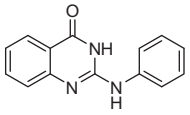
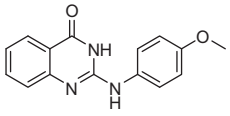
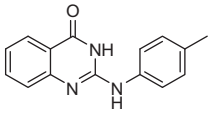
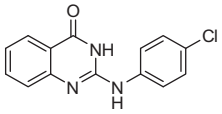
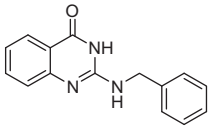
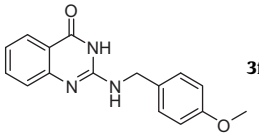
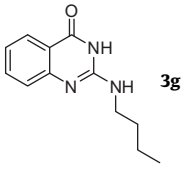
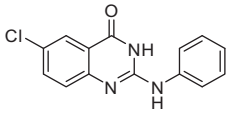
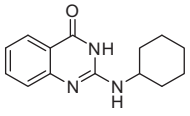
Scheme 1. Possible structure and selectivity in isocyanide insertion reaction.



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

Table 2
Pd-catalyzed synthesis of phenylamino-substituted quinazolinones[a]



Entry	1(Urea)	Quinazolinones (**3a–i**)	Yield[b] (%)
1	**1a**	 **3a**	71
2	**1b**	 **3b**	66
3	**1c**	 **3c**	62
4	**1d**	 **3d**	45
5	**1e**	 **3e**	52
6	**1f**	 **3f**	76
7	**1g**	 **3g**	49
8	**1h**	 **3h**	59
9	**1i**	 **3i**	48
10[c]	**1j**	**3a**	68
11[d]	**1k**	**3a**	0
12[e]	**1a**	**3a**	13

[a] Reaction conditions: urea (**1a**) (1.0 mmol), Isocyanides (1.2 mmol), $Pd(OAc)_2$ catalyst (10 mol %), and base (2.0 mmol) in DMF (5 mL) under N_2 for 12 h at 120° C.
[b] Isolated yield.
[c] Bromourea derivative was used in place of iodo (24 h).
[d] Chlorourea derivative was used in place of iodo.
[e] Cyclohexyl isocyanide was used in place of **2a**.

derivatives which leads to complex **4.** Isocyanide insertion of *tert*-butyl isocyanide on complex **4** leads to Pd(II) species **5**. This intermediate **5** via intramolecular cyclization followed by subsequent reductive elimination provides species **7**, which undergoes a base mediated Mazurciewitcz-Ganesan type rearrangement with de-*tert*-butylation to afford **3** (Scheme 2).[13]

With the optimized condition in hand, we next surveyed the generality of this palladium mediated coupling process (Table 2). We observed that the reaction yields depend slightly upon the electron-withdrawing and -donating groups present in the phenyl ring of urea derivatives. Equally significant isolated yields for urea containing bromides were reported with the same conditions optimized for the iodides (Table 2, entry 10) but higher reaction time was required. Whereas chloro substituted urea derivatives were found to be completely inert toward the isocyanide insertion reaction (Table 2, entry 11). Good yields were observed for the *tert*-butyl isocyanide based insertion reactions (**3a–3i)**, whereas low yield of the product was obtained when cyclohexyl isocyanide was used (Table 2, entry 12). These exciting preliminary results certainly unveil the doors to the rapid synthesis of highly diverse quinazolinones especially in the natural product synthesis.

In summary, we have developed a ligand-free palladium catalyzed reactions for the synthesis of phenylamino-substituted quinazolinone derivatives via isocyanide insertion approach. The strategy allows synthesis of biologically important molecules in a straightforward and atom-economical fashion, which otherwise requires multistep procedures. The applications of this methodology in the synthesis of more complex molecules are currently underway in our group, and results will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.09.027.

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12. A 50 mL Schlenk tube was charged with urea (**1a**) (1 mmol), Cs_2CO_3 (2.0 mmol), and $Pd(OAc)_2$ catalyst (10.0 mol%) in DMF (5 mL). Vacuum was applied and the flask was back-filled with N_2. Isocyanide (1.2 mmol), was added via syringe and the punctured septum was replaced with a new one under a stream of nitrogen. The reaction mixture was stirred at 120 °C in N_2 atmosphere for 12 h. After cooling to room temperature, the mixture was diluted with DMF (5 mL), filtered through a short silica plug (EtOAc rinse), and concentrated using a rotary evaporator. The residue was purified using silica gel chromatography (DCM–MeOH, 95:5) to afford **3a**. *2-(Phenylamino)quinazolin-4(3H)-one (**3a**):* Physical state: solid, mass (EI): m/z = 237 (M^+); ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 7.04 (t, J = 7.2 Hz, 1H), 7.23 (t, J = 7.2 Hz, 1H), 7.35 (t, J = 7.8 Hz, 2H), 7.41 (d, J = 11.4 Hz, 1H), 7.65 (td, J = 1.2 Hz, 7.2 Hz, 1H), 7.77 (d, J = 7.8 Hz, 2H), 7.98 (dd, J = 1.2 Hz, 7.8 Hz, 1H), 8.49 (s, 1H), 9.30 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 118.8, 119.7, 122.9, 123.4, 125.4, 126.4, 129.3, 134.9, 139.5, 148.2, 150.2, 162.1. Anal. calcd for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71, found: C, 70.98; H, 4.54; N, 77.56. IR (KBr): 3298, 3189, 3063, 1647, 1610 cm^{-1}.

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