

Temperature-controlled synthesis of N-acyl anthranilamides and quinazoline-4-ones via Pd-catalysed cascade consisting of isocyanide insertion

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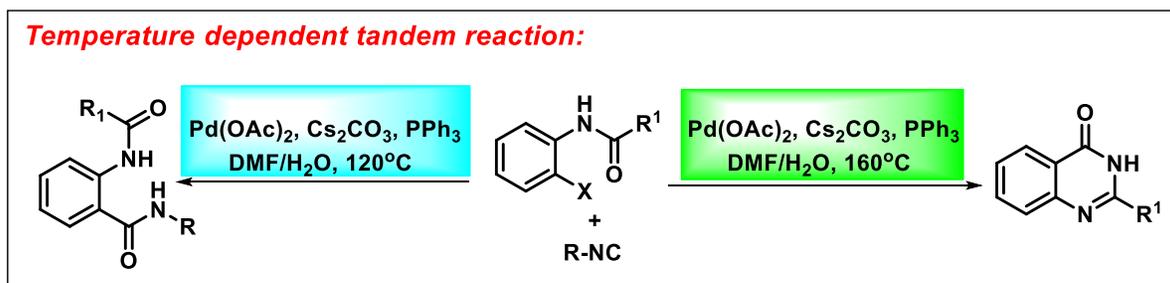
Received 01-02-2019

Accepted 05-20-2019

Published on line 05-24-2019

Abstract

A one step synthesis of functionized N-acyl anthranilamide via Pd-catalyzed carboxamidation of *o*-halo substituted *N*-phenylamide consisting of isocyanide insertion followed by oxidation of the imine intermediate has been achieved successfully. Furthermore, at elevated temperature (160°C) the Pd-catalyzed tandem reaction afforded functionized quinazolin-4-one in a single step without the isolation of N-acyl anthranilamide and proceed through carboxamidation/de-*t*-butylation/cyclodehydration cascade. This work extends the application of isocyanide insertion chemistry for synthesizing diverse N-heterocycles by transition metal catalysed sequential reactions in a single step.



Keywords: N-acyl anthranilamide, quinazoline-4-one, isocyanide, palladium, cascade reactions

Introduction

Transition metal catalysed sequential reactions (tandem) for the syntheses of functionalized heterocycles are on high demand due to the presence of less purification and separation steps and production of fewer numbers of toxic substances throughout the synthesis.¹⁻⁴

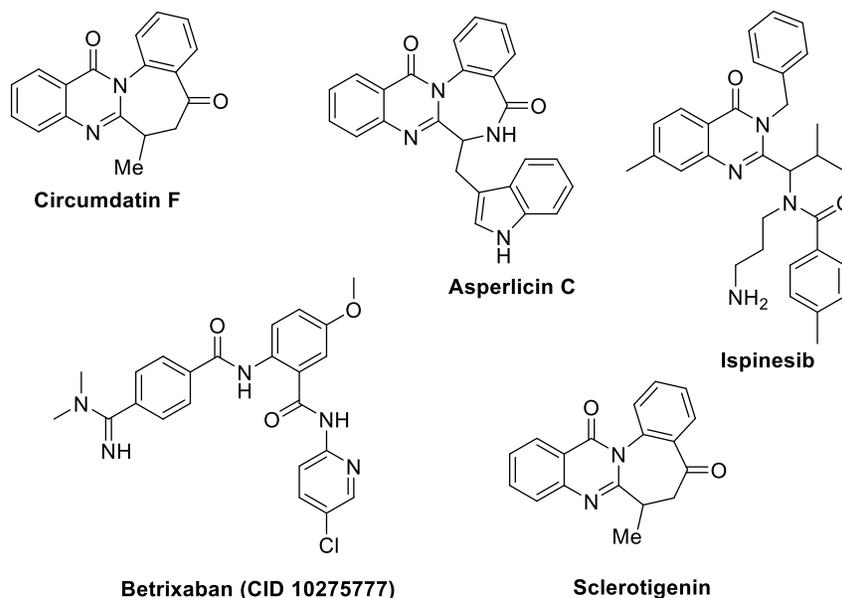


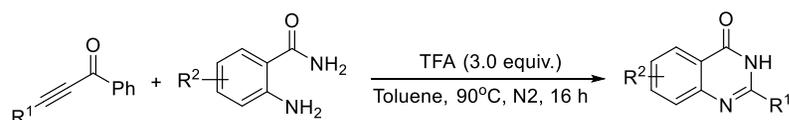
Figure 1. Some biologically active molecules and natural products containing N-acyl anthranilamide and quinazolin-4-one motifs.

Despite the progress in this area,⁵⁻⁷ we are lagging behind in the development of new one step methods proceeds through a sequence of reactions for the synthesis of nitrogen-containing heterocycles, those are ubiquitous and integral pharmacophoric units prevalent in a diverse variety of bioactive natural products, synthetic drugs, pharmaceutical and agrochemicals.⁸⁻⁹ Among these nitrogen-containing heterocycles N-acyl anthranilamide and quinazolin-4-one cores and their derivatives constitute an imperative class of compounds with a diverse therapeutic and pharmacological properties such as antimicrobial, anticonvulsant, anticancer, antimalarial, antihypertensive, anti-inflammatory, anti-diabetic, antitumor, anti-cholinesterase, dihydrofolate reductase inhibition, cellular phosphorylation inhibition, and kinase inhibitory activities, also, they are part of a number of natural products (Figure 1).¹⁰⁻¹⁸ Due to the exhibition of a number of biological activities and part of a number of natural products, the development of new methods for the synthesis of N-acyl anthranilamide and quinazolin-4-one skeleton have grabbed lot of attention in recent years.¹⁹⁻²⁰ In general, we use anthranilic acids for synthesizing corresponding anthranilamide, although, this process is inherently restricted by the limited range of commercially available anthranilic acids.²¹ Additionally, various methods have been reported for the synthesis of N-acyl anthranilamide and quinazolin-4-one skeleton in recent years (Scheme 1).²²⁻²⁵ However, mostly of them have certain drawbacks such as multistep, longer reaction time, the limited selection of commercially available starting materials and lower yields.^{19-20, 22-24} This prompted us to develop a single step synthesis of N-acyl anthranilamide and the quinazolin-4-one skeleton using isocyanide-insertion chemistry.

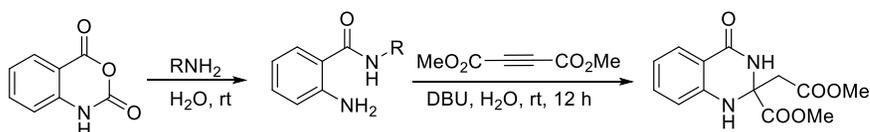
There are many reports about Pd-metal catalyzed aminocarbonylation for the synthesis of amides from

aryl halides,²⁶⁻³⁰ however; the use and handling of toxic carbon monoxide limited the scope of this kind of reaction. In last few years, isocyanides which are isoelectronic with carbon monoxide have been used as synthetic surrogates of CO in Pd-catalysed tandem reactions for synthesizing a broad range of nitrogen-containing heterocycles.³¹⁻³² Previously, we have been also engaged in exploring the applications of isocyanide as precursors and developed new methodologies for the synthesis of highly diverse nitrogen-containing heterocycles.³³⁻³⁴ In continuation of these studies, herein, we reported a synthetic protocol, enabled to furnish functionalized N-acyl anthranilamide and quinazoline-4-one skeleton starting with o-halo substituted N-phenylamide via a temperature dependent Pd-catalyzed cascade consisting of carboxamidation or carboxamidation/de-tertbutylation/cyclodehydration cascade.

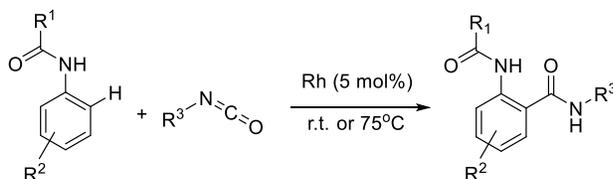
Yang *et. al.*



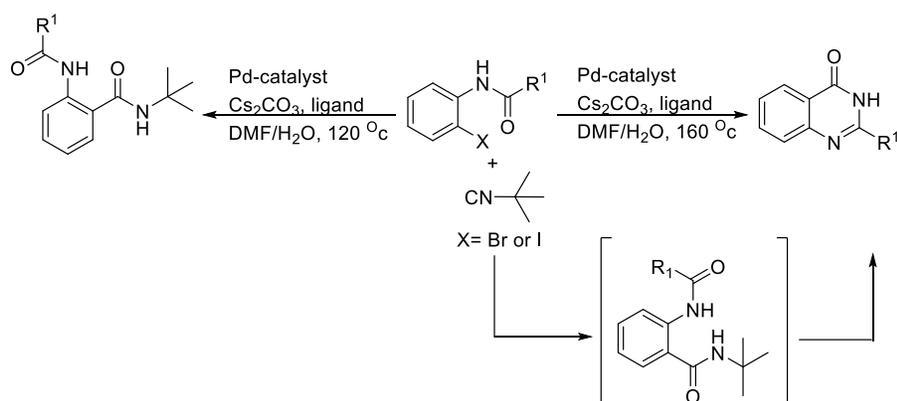
Shafiee *et. al.*



Ellman *et. al.*



Our approach



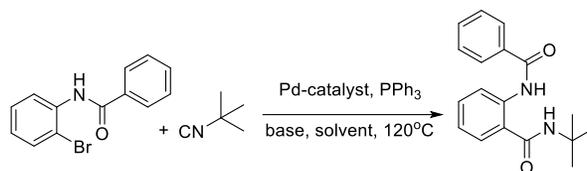
Scheme 1. Recent approaches for the synthesis of N-acyl anthranilamide and quinazolin-4-one.

Results and Discussion

We initiated the study by using amide **1a** and *tert*-butyl isocyanide **2a** as a model substrates for the optimization of palladium-catalyzed carboxamidation reaction. The investigation was carried out using different catalysts, base and solvents (Table 1). The reaction did not proceed in the absence of the Pd catalyst

(Table 1, entry 1). Among the three Pd-catalysts used (PdCl_2 , Pd(PPh)_3 and Pd(OAc)_2), Pd(OAc)_2 was found to be the best and provided the product **3a** in 72% yield in DMF/ H_2O as a solvent at 120 °C (Table 1, entry 4). Furthermore, PdCl_2 and Pd(PPh)_3 furnished inferior yields of product **3a** (Table 1, entry 2 and 3). We next tested the coupling reaction using various bases such as Cs_2CO_3 , K_2CO_3 , Na_2CO_3 , K_3PO_4 and KOtBu in DMF/ H_2O at 120 °C, with Pd(OAc)_2 as a catalyst, among these bases Cs_2CO_3 was found to be the most effective base (Table 1, entry 4). Using Pd(OAc)_2 as catalyst and Cs_2CO_3 as base in DMSO/ H_2O provided slightly poor yield of **3a** (Table 1, entry 9), while using toluene and CH_3CN under the same conditions furnished **3a** in only poor yields (Table 1, entry 10 and 11). The procedure was unfavourable when base was omitted from the reaction (Table 1, entry 12). Further optimization revealed that PPh_3 was essential in this reaction as well. Without PPh_3 , the yield decreased to 49%. When tested the carboxamidation reaction in dry DMF as solvent, the efficacy of carboxamidation reaction was affected and gave product only in trace amount (Table 1, entry 13).

Table 1. Optimization of conditions for N-acyl anthranilamide synthesis

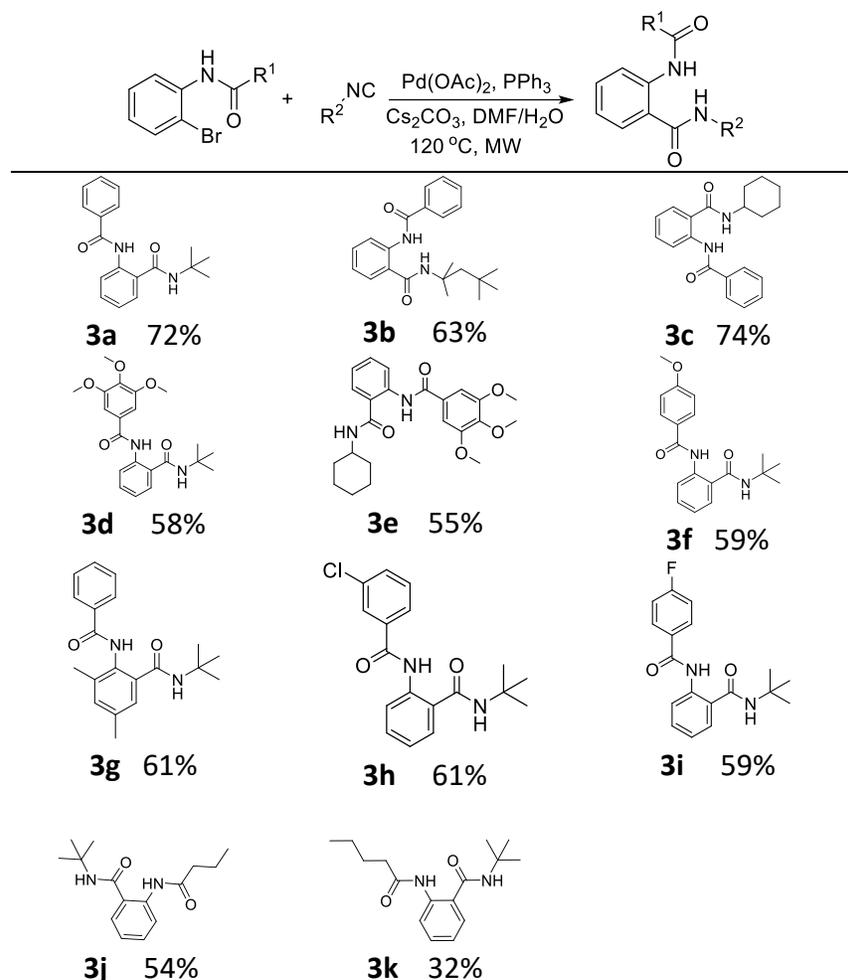


Entry	catalyst	base	ligand	yield % b
1	-	Cs_2CO_3	DMF/ H_2O	0 ^c
2	PdCl_2	Cs_2CO_3	DMF/ H_2O	33
3	Pd(PPh)_3	Cs_2CO_3	DMF/ H_2O	59
4	Pd(OAc)_2	Cs_2CO_3	DMF/ H_2O	72
5	Pd(OAc)_2	K_2CO_3	DMF/ H_2O	59
6	Pd(OAc)_2	K_3PO_4	DMF/ H_2O	41
7	Pd(OAc)_2	KOtBu	DMF/ H_2O	32
8	Pd(OAc)_2	Na_2CO_3	DMF/ H_2O	53
9	Pd(OAc)_2	Cs_2CO_3	DMSO/ H_2O	41
10	Pd(OAc)_2	Cs_2CO_3	Toluene/ H_2O	19
11	Pd(OAc)_2	Cs_2CO_3	$\text{CH}_3\text{CN}/\text{H}_2\text{O}$	31
12	Pd(OAc)_2	-	DMF/ H_2O	0 ^d
13	Pd(OAc)_2	Cs_2CO_3	DMF	trace

^aReaction conditions: All reactions were performed either in microwave tube or 10 mL round bottom flask using *N*-(2-bromophenyl)benzamide **1a** (1.0 equiv.), *t*-butyl isocyanide **2a** (1.1 equiv.), Pd-catalyst (5 mol %), PPh_3 (5 mol %) and base (1.2 equiv.), solvent (0.5 mL of H_2O in 1.5 mL of solvent) at 120°C for 15-20 min in MW or 4-5 hrs at conventional heating. ^bisolated yield.

It is interesting to note that at room temperature there was no conversion but the reaction was completed within 15-20 min under MW conditions at 120 °C, while in the absence of MW irradiations it took 4-5 h to reach the completion. After having optimized reaction conditions for the carboxamidation of *N*-(2-bromophenyl)benzamide **1a** with *tert*-butyl isocyanide **2a**, we further explore the reaction scope for other substituted *N*-phenylamide with a range of isocyanides (Table 2). In addition to *t*-butyl isocyanide, the carboxamidation of **1a** with *tert*-octyl and cyclohexyl isocyanide substrates provided *N*-acyl anthranilamide products **3b** and **3c** in good yields (63 and 74%, respectively) when employing 5 mol % of Pd(OAc)₂ in DMF/H₂O under microwave irradiation for 20 min. Next, we investigated the scope of substituted *N*-phenylamide (Table 2). To our delight, many substituents at different positions on the phenyl group are compatible with the reaction conditions, producing the corresponding products in good yields (Table 2, entries **3d-3i**). For electron-donating group such as 3,4,5-trimethoxy, 4-methoxy or 2, 4-methyl substituted phenyl amide with *tert*-butyl or cyclohexyl isocyanides reactions work nicely and gave 58%, 55%, 59% and 61% yield respectively (Table 2, entry **3d-3g**). Also, *m*-Cl and *p*-F on phenyl group were tolerated well and gave 61% and 59% yield respectively.

Table 2. Substrate scope of Pd-catalyzed cascade for the synthesis of diverse *N*-acyl anthranilamide derivative^a

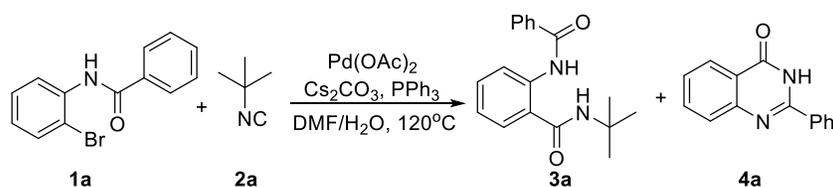


^aReaction conditions: Pd(OAc)₂ (5 mol %), Cs₂CO₃ (1.2 equiv.), DMF/H₂O (2 mL), MW, 120 °C, reaction time 20 min. ^bYields refer to isolated products.

(Table 2, entry **3h & 3i**). Moreover, we investigated *N*-phenylamide bearing an alkyl group such as *t*-butyl and *n*-propyl instead of phenyl group and the reaction gave corresponding products in decent yield (Table 2, entry **3j-3n**), however slightly lower yield obtained compared to phenyl group.

There are few methods available for synthesizing quinazolin-4-one by the cyclodehydration reaction of *N*-acyl anthranilamides. Although, we envisaged that by conducting the Pd-catalyzed reaction at elevated temperature, both the carboxamidation and cyclodehydration sequence could be accomplished in a single step. To synthesize quinazolin-4-one selectively, we did temperature variations under previously optimized conditions (Table 3). Increasing the temperature of the reaction between **1a** and **2a** under the optimized catalyst conditions to 140°C and monitoring the reaction by ¹H NMR, *N*-acyl anthranilamide product **3a** was formed in 42% yield along with the quinazoline-4-one (**4a**) in 21% yield (Table 3, entry 3). When we elevated the temperature upto 160°C, quinazoline-4-one was formed selectively (Table 3, entry 5). Also, we found that in the absence of Pd-catalyst, heating the isolated *N*-acyl anthranilamide **3a** gave quinazoline-4-one **4a** only in trace amount. This result suggested to us that cyclodehydration of **3a** to **4a** is assisted by the Pd-catalyst rather than being solely thermally induced.

Table 3. Optimization of condition for quinazolinone synthesis^a



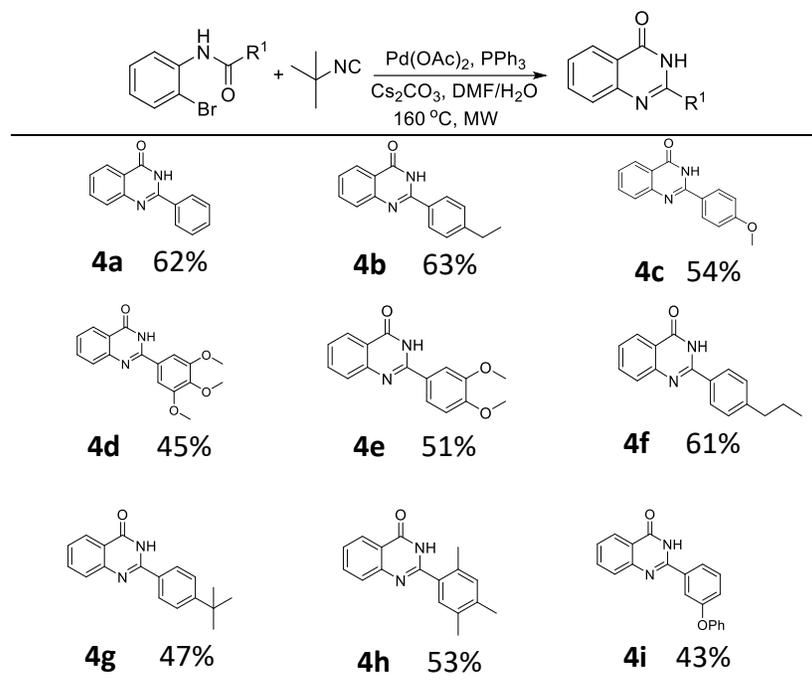
Entry	Variation from the "standard conditions" ^a	yield% 3a	yield% 4a
1.	None	72%	0%
2.	Without Pd(OAc) ₂	trace	n. r.
3.	At 140°C	42%	21%
4.	Without H ₂ O	trace	n. r.
5.	At 160°C	trace	62%

^aReaction conditions: reactions were performed in a microwave vial using *N*-(2-bromophenyl)benzamide **1a** (1.0 equiv.), *t*-butylisocyanide **2a** (1.1 equiv.), Pd-catalyst (5 mol %), PPh₃ (5 mol %) and Cs₂CO₃ (1.2 equiv.), solvent (0.5 mL of H₂O in 1.5 mL DMF) at different temperatures for 15-20 min in MW, yields refer to isolated products.

After optimizing the reaction conditions for the selective synthesis of quinazolinone by the reaction of **1a** with **2a**, we investigated the scope of one step cascade reaction for a broad range of *N*-phenylamides. A number of substituents at different positions on the phenyl group such as alkyl, methoxy and phenyl compatible with the optimized reaction conditions, gave the corresponding products **4a-4i** in good yields (Table 4, entries **4a-4i**). Furthermore, when we tested cyclohexyl isocyanide in place of *t*-butyl isocyanide, no quinazolinone

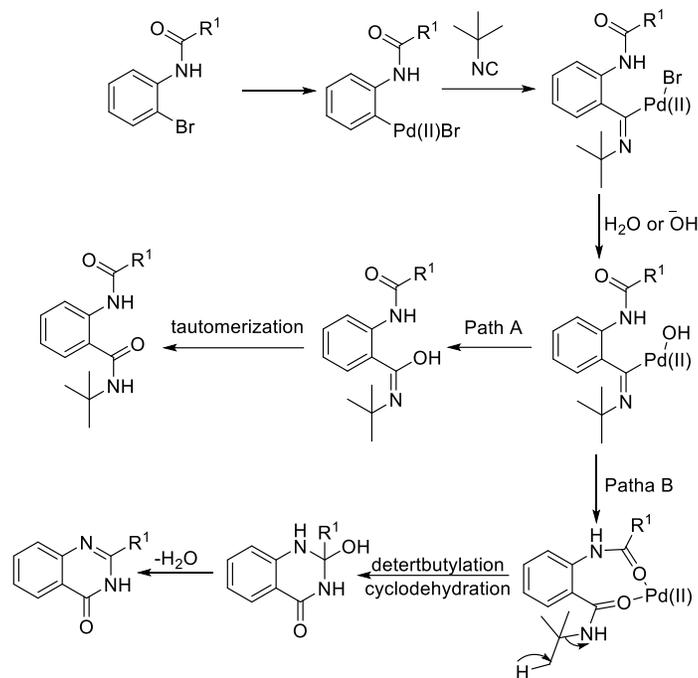
formed, N-acyl anthranilamide was the product. Also, this experiment indirectly supports de-*tert*-butylation (step viii, scheme 2) during the synthesis of quinazoline-4-one.

Table 4. Substrate scope of Pd-catalyzed cascade for synthesis of diverse quinazolinone derivatives^a



^aReaction conditions: Pd(OAc)₂ (5 mol %), Cs₂CO₃ (1.2 equiv.), DMF/H₂O (1.7 mL), MW, 160 °C, reaction time 20 min. Yields refer to isolated products.

A plausible mechanism for anthranilamide and quinazolinone synthesis is proposed in Scheme 2. Thus, oxidative insertion of Pd(0) into the *o*-halo substituted *N*-phenylamide (**i**) leads to the intermediate (**ii**) which on insertion of *t*-butyl isocyanide (2a) leads to Pd(II) species (**iii**), Intermediate (**iii**) via fast ligand exchange with water gives intermediate (**iv**), which can react through two different pathways which depend on reaction temperature. At lower temperature (120°C) pathway A is followed, reductive elimination and subsequent tautomerization, to give N-acyl anthranilamide as product and Pd(0) for another catalytic cycle. At higher temperature (160°C) reaction follows path B, which goes through de-*tert*-butylation and subsequent cyclodehydration in the presence of Pd-catalyst to furnish quinazolinone product.



Scheme 2. Plausible mechanism for anthranilamide and quinazolinone synthesis.

Conclusions

In summary, we have reported the first synthesis of N-acyl anthranilamide and quinazolin-4-one derivatives via Pd-catalyzed cascade reaction consisting of isocyanide insertion into diverse *o*-halo substituted N-phenylamides. This cascade reaction allows the synthesis of N-acyl anthranilamide at 120°C by use of easily available and less expensive starting materials, while at elevated temperature (160°C) provides quinazolin-4-one as the only detectable product. Additionally, a broad range of substrates are tolerated in this protocol which provides a diverse library of N-acyl anthranilamide and quinazolin-4-one derivatives for combinatorial and medicinal chemistry use. Moreover, reported work here contributes to expand the growing number of transition metal catalysed sequential reactions in one-pot for the synthesis of functionalized nitrogen-containing heterocycles.

Experimental Section

General. All reagents and solvents were purchased from commercial sources and used without purification. NMR spectra were recorded on a Bruker spectrometer at 300 (400) and 75 (100) MHz, respectively in deuterated solvents with TMS as internal reference (chemical shifts δ in ppm, coupling constant J in Hz.). Multiplicities are reported as follows: singlet (s), doublet (d), triplet (t), multiplet (m), and broad singlet (brs). Mass spectra and HRMS were taken in the ESI positive ion mode. The reaction progress was monitored by thin layer chromatography (TLC) on pre-coated silica gel plates. Column chromatography was performed over Merck silica gel (230-400 flash). All compounds were characterized by TLC, ^1H NMR and ^{13}C NMR and HRMS.

General procedure for the synthesis of substituted N-acyl anthranilamides(3a-3k). Substituted N-phenylamide **1** (1 equiv.), isocyanide **2** (1.1 equiv.), Pd(OAc)₂ (5 mol %), Cs₂CO₃ (1.2 equiv.), PPh₃(5 mol %) and DMF:H₂O (3:1) as a solvent were added in a 10 mL microwave vial containing a stirring bar, the vial was sealed tightly with a Teflon cap and placed in microwave cavity for 15-20 min at a pre-selected temperature of 120 °C. After completion of the reaction as indicated by TLC, the resulting mixture was filtered through a pad of celite, and the celite was rinsed with EtOAc. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel (eluent: hexane/ EtOAc) affording the corresponding coupling product **3a-3k** in 74-32% yields.

General procedure for the synthesis of substituted quinazoline-4-one (4a-4i). Substituted N-phenylamide **1** (1 equiv.), isocyanide **2** (1.1 equiv.), Pd(OAc)₂ (5 mol %), Cs₂CO₃ (1.2 equiv.), PPh₃(5 mol %) and DMF:H₂O (3:1) as a solvent were added in a 10 mL microwave vial containing a stirring bar, the vial was sealed tightly with a Teflon cap and placed in a microwave cavity for 15-20 min at a pre-selected temperature of 160 °C. After completion of the reaction as indicated by TLC, the resulting mixture was filtered through a pad of celite, and the celite was rinsed with EtOAc. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel (eluent: hexane/ EtOAc) affording the corresponding coupling products **4a-4i** in 63-43% yields.

2-Benzamido-N-tert-butylbenzamide (3a). Solid, Yield 72%, mp 143-146 °C, FT-IR (KBr) ν (cm⁻¹): 3425, 2946, 2324, 1627, 1106, 759, ¹H NMR (400 MHz, CDCl₃): δ 11.95 (brs, 1H), 8.77 (d, *J* 8.4 Hz, 1H), 8.06-8.04 (m, 2H), 7.58-7.44 (m, 5H), 7.09 (t, *J* 7.2 Hz, 1H), 6.16 (br s, 1H), 1.52 (s, 9H) ppm, ¹³C NMR (100 MHz, CDCl₃): 169.0, 165.5, 139.5, 134.8, 132.2, 131.7, 128.7, 127.4, 126.4, 122.7, 122.3, 121.6, 52.2, 28.7 ppm, HRMS (ESI) Calcd. for C₁₈H₂₀N₂O₂ [M+H]⁺ 297.1525 Found 297.1595.

2-Benzamido-N-(2,4,4-trimethylpentan-2-yl)benzamide (3b). Solid, Yield 63%, ¹H NMR (400 MHz, CDCl₃): δ 11.9 (brs, 1H), 8.76 (d, *J* 8.0 Hz, 1H), 8.05 (d, *J* 6.8 Hz, 2H), 7.58-7.42 (m, 5H), 7.08 (t, *J* 7.2 Hz, 1H), 6.20 (brs, 1H), 1.92 (s, 2H), 1.57 (s, 6H), 1.07 (s, 9H) ppm, ¹³C NMR (100 MHz, CDCl₃): 168.8, 165.4, 139.3, 134.8, 132.0, 131.7, 128.7, 127.3, 126.3, 122.8, 122.7, 121.7, 56.1, 51.5, 31.7, 31.5, 29.1 ppm, HRMS (ESI) Calcd. for C₂₂H₂₈N₂O₂ [M+H]⁺ 353.2151 Found 353.2221.

2-Benzamido-N-cyclohexylbenzamide (3c). Solid, Yield 74%, ¹H NMR (300 MHz, CDCl₃): δ 12.0 (brs, 1H), 8.77 (d, *J* 8.1 Hz, 1H), 8.05 (d, *J* 5.7 Hz, 2H), 7.55-7.49 (m, 5H), 7.05 (t, *J* 7.2 Hz, 1H), 6.43 (brs, 1H), 4.00-3.97 (m, 1H), 2.07-2.04 (m, 2H), 1.81-1.67 (m, 3H), 1.51-1.21 (m, 5H) ppm, ¹³C NMR (75 MHz, CDCl₃): 168.3, 165.5, 139.7, 134.8, 132.4, 131.8, 128.7, 127.3, 126.6, 122.7, 121.5, 121.0, 48.8, 33.0, 25.4, 24.9 ppm, HRMS (ESI) Calcd. for C₂₀H₂₂N₂O₂ [M+H]⁺ 323.1681 Found 323.1751

N-(2-(tert-Butylcarbamoyl)phenyl)-3,4,5-trimethoxybenzamide (3d). Solid, Yield 58%, ¹H NMR (400 MHz, CDCl₃): δ 12.1 (brs, 1H), 8.79 (d, *J* 8.4, 1H), 7.51-7.43 (m, 2H), 7.32 (s, 2H), 7.08 (t, *J* 7.6 Hz, 1H), 6.13 (brs, 1H), 3.97 (s, 6H), 3.92 (s, 3H), 1.49 (s, 9H) ppm, ¹³C NMR (100 MHz, CDCl₃): 169.3, 165.2, 153.3, 141.2, 140.1, 132.6, 130.4, 126.6, 122.8, 121.7, 121.4, 104.8, 61.1, 56.3, 52.4, 28.9 ppm, HRMS (ESI) Calcd. for C₂₁H₂₆N₂O₅ [M+H]⁺ 387.1842 Found 387.1917.

N-(2-(Cyclohexylcarbamoyl)phenyl)-3,4,5-trimethoxybenzamide (3e). Solid, Yield 55%, ¹H NMR (300 MHz, CDCl₃): δ 12.1 (brs, 1H), 8.88-8.47 (m, 1H), 7.54-7.48 (m, 2H), 7.30 (s, 2H), 7.11 (t, *J* 9.6 Hz, 1H), 6.28 (brs, 1H), 3.98 (s, 6H), 3.93 (s, 3H), 3.98-3.93 (m, 1H), 2.05-2.02 (m, 2H), 1.80-1.66 (m, 3H), 1.49-1.20 (m, 5H) ppm, ¹³C NMR (75 MHz, CDCl₃): 168.3, 165.2, 153.2, 141.0, 139.8, 132.5, 130.3, 126.4, 122.7, 121.3, 120.9, 104.7, 60.9, 56.2, 48.8, 32.9, 25.4, 24.8 ppm, HRMS (ESI) Calcd. for C₂₃H₂₈N₂O₅ [M+H]⁺ 413.1998 Found 413.2073.

N-tert-Butyl-2-(4-methoxybenzamido)benzamide (3f). Solid, Yield 59%, ¹H NMR (400 MHz, CDCl₃): δ 11.78 (brs, 1H), 8.69 (d, *J* 8.4 Hz, 1H), 7.98 (d, *J* 8.8 Hz, 2H), 7.44-7.39 (m, 2H), 7.00-6.94 (m, 3H), 6.29 (brs, 1H), 3.86

(s, 3H), 1.50 (s, 9H) ppm, ^{13}C NMR (100 MHz, CDCl_3): 169.3, 165.2, 162.6, 139.7, 132.2, 129.4, 127.4, 126.8, 122.6, 122.4, 121.6, 114.1, 55.6, 52.3, 28.7 ppm, HRMS (ESI) Calcd. for $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$ 327.1630 Found 327.1705.

2-Benzamido-*N*-tert-butyl-3,5-dimethylbenzamide (3g). Solid, Yield 61%, ^1H NMR (400 MHz, CDCl_3): δ 9.88 (brs, 1H), 8.16 (d, J 7.5 Hz, 2H), 7.58-7.46 (m, 3H), 7.00 (s, 1H), 6.95 (s, 1H), 6.50 (brs, 1H), 2.25 (s, 3H), 2.19 (s, 3H), 1.25 (s, 9H) ppm, ^{13}C NMR (100 MHz, CDCl_3): 169.2, 167.4, 136.6, 136.5, 135.4, 133.8, 132.6, 131.7, 130.3, 128.4, 127.8, 125.3, 51.6, 28.4, 20.8, 18.4 ppm, HRMS (ESI) Calcd. for $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 325.1838 Found 325.1912.

***N*-tert-Butyl-2-(3-chlorobenzamido)benzamide (3h).** Solid, Yield 61%, ^1H NMR (400 MHz, CDCl_3): δ 12.0 (s, 1H), 8.69 (s, J 8.4 Hz, 1H), 8.03 (s, 1H), 7.87 (d, J 7.6 Hz, 1H), 7.53-7.42 (m, 4H), 7.04 (t, J 7.6 Hz, 1H), 6.33 (br s, 1H), 1.53 (s, 9H) ppm, ^{13}C NMR (100 MHz, CDCl_3): 169.2, 164.3, 139.3, 136.9, 135.1, 132.3, 131.9, 130.2, 128.3, 126.8, 125.2, 123.2, 122.4, 121.7, 52.4, 28.9 ppm, HRMS (ESI) Calcd. for $\text{C}_{18}\text{H}_{19}\text{ClN}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 331.1135 Found 331.1212.

***N*-tert-Butyl-2-(4-fluorobenzamido)benzamide (3i).** Solid, Yield 59%, ^1H NMR (400 MHz, CDCl_3): δ 11.9 (brs, 1H), 8.72 (d, J 8.4 Hz, 1H), 8.05-8.02 (m, 2H), 7.49-7.42 (m, 2H), 7.20 (t, J 8.4 Hz, 2H), 7.06 (t, J 7.6 Hz, 1H), 6.19 (brs, 1H), 1.50 (s, 9H) ppm, ^{13}C NMR (100 MHz, CDCl_3): 169.2, 164.5, 139.7, 132.4, 131.3, 131.2, 130.0, 129.9, 126.7, 123.0, 122.2, 121.7, 116.0, 115.8, 52.4, 28.9 ppm, HRMS (ESI) Calcd. for $\text{C}_{18}\text{H}_{19}\text{FN}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 315.1431 Found 315.1506.

***N*-tert-Butyl-2-butyramidobenzamide (3k).** Solid, Yield 54%, ^1H NMR (400 MHz, CDCl_3): 10.8 (brs, 1H), 8.4 (s, 1H), 7.39 (t, J 5.4 Hz, 2H), 7.00 (s, J 5.4 Hz, 1H), 6.16 (brs, 1H), 2.35 (t, J 7.2 Hz, 2H), 1.76 (t, J 7.2 Hz, 2H), 1.45 (s, 9H), 1.02-0.96 (m, 3H) ppm, ^{13}C NMR (75 MHz, CDCl_3): 172.1, 169.0, 139.2, 132.1, 126.7, 122.6, 122.4, 121.7, 52.2, 40.5, 28.9, 19.2, 13.9 ppm, HRMS (ESI) Calcd. for $\text{C}_{15}\text{H}_{22}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 263.1681 Found 263.1757.

***N*-tert-Butyl-2-pentanamidobenzamide (3j).** Solid, Yield = 78%, ^1H NMR (400 MHz, CDCl_3): 10.8 (brs, 1H), 8.52 (d, J 8.4 Hz, 1H), 7.51-7.36 (m, 2H), 7.03 (t, J 7.6 Hz, 1H), 6.16 (brs, 1H), 2.40 (t, J 7.6 Hz, 2H), 1.76-1.64 (m, 2H), 1.48 (s, 9H), 1.45-1.36 (m, 2H), 0.97 (t, J 7.6 Hz, 3H) ppm, ^{13}C NMR (75 MHz, CDCl_3): 172.1, 168.8, 139.1, 131.9, 126.4, 122.4, 122.2, 121.5, 52.0, 38.1, 28.7, 27.6, 22.3, 13.7 ppm, HRMS (ESI) Calcd. for $\text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 277.1838 Found 277.1904.

2-Phenylquinazolin-4(3H)-one (4a). Solid, Yield = 62%, mp 176-178 $^\circ\text{C}$ FT-IR (KBr) ν (cm^{-1}): 3425, 2943, 2354, 1637, 1123, 761, ^1H NMR (400 MHz, DMSO-d_6): 12.5 (brs, 1H), 8.20 (t, J 8.4 Hz, 3H), 7.86 (t, J 7.6 Hz, 1H), 7.76 (d, J 8.0 Hz, 1H), 7.59-7.50 (m, 4H) ppm, ^{13}C NMR (100 MHz, DMSO-d_6): 162.7, 152.7, 149.2, 135.0, 133.1, 131.8, 129.0, 128.2, 127.9, 127.0, 126.3, 121.4 ppm, HRMS (ESI) Calcd. for $\text{C}_{14}\text{H}_{10}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$ 223.0793 Found 223.0864.

2-(4-Ethylphenyl)quinazolin-4(3H)-one(4b). Solid, Yield 63%, ^1H NMR (300 MHz, CDCl_3): δ 11.5 (brs, 1H), 8.36 (d, J 5.8 Hz, 1H), 8.21 (d, J 6.0 Hz, 2H), 7.86-7.79 (m, 2H), 7.53-7.51 (t, J 5.1 Hz, 1H), 7.50 (d, J 6.0 Hz, 2H), 2.81 (q, J 5.7 Hz, 2H), 1.35 (t, J 5.7 Hz, 3H) ppm, ^{13}C NMR (75 MHz, CDCl_3): δ 163.7, 151.7, 149.6, 148.4, 134.8, 130.2, 128.6, 127.9, 127.4, 126.5, 126.4, 28.8, 15.3 ppm.

2-(4-Methoxyphenyl)quinazolin-4(3H)-one (4c). Solid, Yield 54%, ^1H NMR (400 MHz, DMSO-d_6): δ 12.4 (brs, 1H), 8.21-8.13 (m, 3H), 7.84 (t, J 8.4 Hz, 1H), 7.72 (d, J 8.0 Hz, 1H), 7.51 (t, J 8.0 Hz, 1H), 7.10 (d, J 8.8 Hz, 2H), 3.88 (s, 3H) ppm, ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.3, 161.8, 151.8, 148.9, 134.5, 129.4, 127.3, 126.1, 125.7, 124.7, 120.7, 113.9, 55.4 ppm, HRMS (ESI) Calcd. for $\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 253.0899 Found 253.0970.

2-(3,4,5-Trimethoxyphenyl)quinazolin-4(3H)-one (4d). Solid, Yield 45%, ^1H NMR (400 MHz, DMSO-d_6): 8.58 (d, J 8.4 Hz, 1H), 8.37 (brs, 1H), 7.64-7.62 (m, 2H), 7.26-7.22 (m, 1H), 7.16 (s, 2H), 3.95 (s, 6H), 3.93 (s, 3H) ppm, ^{13}C NMR (100 MHz, DMSO-d_6): 165.3, 153.7, 142.1, 140.9, 134.5, 132.2, 129.2, 124.4, 121.1, 116.7, 104.7, 102.3, 61.1, 56.5 ppm, HRMS (ESI) Calcd. for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$ 313.1110 Found 313.1185.

2-(3,4-Dimethoxyphenyl)-3,4-dihydroquinazolin-4-one (4e). Solid, Yield 51%, ^1H NMR (400 MHz, CDCl_3): δ 7.96 (d, $J=6.4$ Hz, 1H), 7.38-7.34 (m, 1H), 7.23 (brs, 1H), 7.08-7.05 (m, 1H), 6.94-6.88 (m, 2H), 6.71 (d, $J=7.6$ Hz, 1H), 3.93 (s, 6H) ppm, ^{13}C NMR (100 MHz, CDCl_3): δ 164.8, 150.4, 149.6, 147.3, 134.0, 130.9, 128.7, 120.1, 119.7, 114.5, 110.9, 109.8, 69.0, 56.0 ppm.

2-(4-Propylphenyl)-3,4-dihydroquinazolin-4-one (4f). Solid, Yield 61%, ^1H NMR (400 MHz, CDCl_3): δ 11.26 (brs, 1H), 8.36 (d, J 7.6 Hz, 1H), 8.17 (d, J 8.0 Hz, 2H), 7.86-7.79 (m, 2H), 7.53 (d, J 6.8 Hz, 1H), 7.42 (d, J 8.4 Hz, 2H), 2.74-2.70 (m, 2H), 1.78-1.69 (m, 2H), 1.02 (m, 3H) ppm, ^{13}C NMR (100 MHz, CDCl_3): δ 163.5, 151.7, 149.6, 146.9, 134.8, 130.2, 129.2, 127.9, 127.1, 126.6, 126.4, 37.9, 24.3, 13.7 ppm.

2-(4-tert-Butylphenyl)-3,4-dihydroquinazolin-4-one (4g). Solid, Yield 47%, ^1H NMR (400 MHz, CDCl_3): δ 11.3 (brs, 1H), 8.37 (d, $J=7.2$ Hz, 1H), 8.20 (d, J 7.2 Hz, 2H), 7.87-7.80 (m, 2H), 7.63 (d, J 8.4 Hz, 2H), 7.54-7.50 (m, 1H), 1.41 (s, 9H) ppm, ^{13}C NMR (100 MHz, CDCl_3): δ 163.8, 155.2, 151.7, 149.6, 134.8, 129.9, 127.9, 127.1, 126.5, 126.3, 126.0, 35.0, 31.2 ppm.

2-(2,4,5-Trimethylphenyl)-3,4-dihydroquinazolin-4-one (4h). Solid, Yield 53%, ^1H NMR (400 MHz, CDCl_3): δ 9.94 (brs, 1H), 8.31 (d, J 8.0 Hz, 1H), 7.81 (d, J 3.6 Hz, 2H), 7.53-7.49 (m, 1H), 7.36 (s, 1H), 7.12 (s, 1H), 2.48 (s, 3H), 2.31 (s, 6H) ppm, ^{13}C NMR (100 MHz, CDCl_3): δ 162.8, 153.6, 149.2, 139.4, 134.7, 134.5, 133.9, 132.8, 130.9, 129.8, 127.8, 126.7, 126.3, 120.6, 19.6, 19.1, 1.02 ppm.

2-(3-Phenoxyphenyl)-3,4-dihydroquinazolin-4-one (4i). Solid, Yield = 43%, ^1H NMR (400 MHz, CDCl_3): δ 11.38 (brs, 1H), 8.26 (s, 1H), 7.99-7.95 (m, 2H), 7.82-7.81 (m, 2H), 7.58-7.10 (m, 8H) ppm, ^{13}C NMR (100 MHz, CDCl_3): δ 163.6, 157.8, 156.9, 151.0, 149.2, 134.9, 134.7, 130.4, 129.9, 128.0, 126.9, 126.4, 123.6, 122.2, 122.1, 118.9, 118.0 ppm.

Acknowledgements

We acknowledge the financial support from Department of Science and Technology, India (DST/INSPIRE/04/2017/000095).

Supplementary Material

The copies of ^1H NMR and ^{13}C NMR spectra of all synthesized compounds presented in the Supplementary Material.

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