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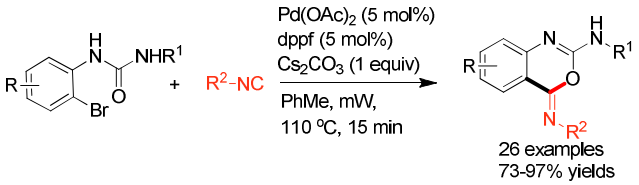
The palladium-catalysed isocyanide insertion in 2-bromophenylureas leads to the formation of 4-substituted imino *4H*-benzo[*d*][1,3]oxazin-2-amines via C-O cross coupling reaction of the intermediate imidoylpalladium species.



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Microwave-assisted Palladium-catalysed isonitrile insertion in 2-bromophenylureas for efficient synthesis of 4-substituted imino *4H*-benzo[*d*][1,3]oxazin-2-amines

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A general route to the synthesis of 4-substituted imino *4H*-benzo[*d*][1,3]oxazin-2-amines via palladium-catalysed isonitrile insertion in 2-bromophenylureas succeeded by a C-O cross-coupling of the intermediate imidoylpalladium species under microwave irradiation is reported.

Recently, we have disclosed palladium-catalysed isocyanide insertion into 2-bromophenylthioureas followed by cross coupling reaction by the thiol group as a novel approach to 4-substitutedimino-4*H*-benzo[*d*][1,3]thiazin-2-amines.[1] Based on the results of this protocol, we considered investigating similar palladium-catalysed isocyanide insertion into 2-bromophenylureas which would allow direct synthesis of 4-substituted imino *4H*-benzo[*d*][1,3]oxazin-2-amines in one-pot. Our reasoning to anticipate the formation of *4H*-benzo[*d*][1,3]oxazin-2-amine was influenced by very recent work of Li and Wu who have reported palladium-catalyzed carbonyl insertion in *N*-(*o*-bromoaryl)amides for the synthesis of benzoxazinones.[2] Earlier Wu and Beller et al.[3] have demonstrated similar palladium-catalyzed carbonylative synthesis of substituted 2-(phenylamino)-4H-benzo[*d*][1,3]oxazin-4-ones from 2-bromoanilines and isocyanates whereas Lioyd-Jones and Brooker-Milburn and co-workers have reported palladium-catalyzed *ortho*-selective carbonylation of *N*-phenylurea derivatives for preparing 2-substitutedamino-benzoxazin-4-ones (Fig. 1).[4] They also reported that in the presence of TsOH in methanol/THF as medium, methanolysis of the imidate takes place leading to the isolation of anthranillate in excellent yields. More recently, Orru and Ruijter and co-workers reported efficient synthesis of 2-aminobenzoxazin-4-ones via palladium-catalyzed oxidative coupling of isonitrile with anthranilic acid.[5]

The 2-substitutedamino-benzoxazin-4-ones are considered important as they are endowed with diverse pharmacological activities including antiviral, antiobesity, cardiovascular, and anti-inflammatory.[6] However, as indicated by Beller[3] and later by Ruijter,[4] the synthetic methodologies for their preparation are rare.[7-8] A careful search of the literature revealed that only two reports describe the synthesis of 4*H*-3,1-benzoxazine-4-imines. The first one relied upon aza-Wittig reaction between iminophospharanes derived from *N*-substituted *ortho*-azidobenzamides and isocyanates whereas the more recent synthesis was accomplished from *ortho*-cyanoanilides and

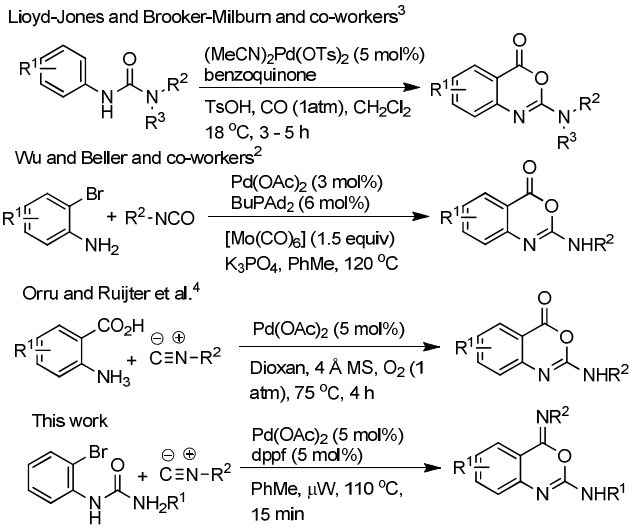


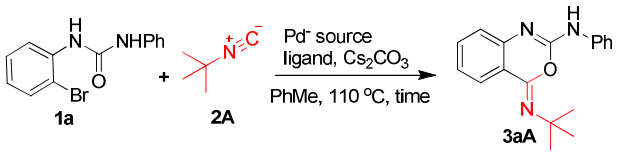
Fig. 1 Different strategies for the synthesis of *4H*-benzo[*d*][1,3]oxazin-2-amines

diaryliodonium triflates via copper-mediated oxidative arylation–cyclization.[9-10] In view of the current interest in palladium-catalyzed isonitrile insertion in the C-halogen bond for obtaining diverse heterocycles[11] we considered exploring our strategy and we present the details of the results herein.

Our study commenced with the reaction of 1.0 equiv of 1-(2-bromophenyl)-3-phenylurea **(1a)** with 1.5 equiv of *tert*-butyl isonitrile **2A** in the presence of 10 mol% of $Pd(OAc)_2$, 10 mol% of dppf and 2.0 equiv of Cs_2CO_3 in dry toluene under nitrogen atmosphere by heating at reflux as reported earlier.[1] The reaction was complete in 12 h to afford a major product in 62% yield as white solid. Based on the spectroscopic analysis, the structure of the product was established as 4-(*tert*-butylimino)-*N*-phenyl-4*H*-benzo[*d*][1,3]oxazin-2-amine **3aA** (Table 1, entry 1). The presence of *tert*-butyl group inferred that hydrolysis of the imino group to carbonyl group did not occurred during the course or work up of the reaction. In our effort to explore the possibility of improving the isolated yield of the product, reaction was conducted under different conditions and the results are summarized in Table 1. This short screening revealed that increasing the amount of $Pd(OAc)_2$ to 20 mol% did not increase

the yield of **3aA** whereas changing the ligand from dppf to PCy_3

Table 1. Optimization of the palladium-catalysed isocyanide insertion in 2-bromophenylurea



Entry[a]	[Pd] source (mol%)	Ligand (mol%)	Cs_2CO_3 (equiv)	Heating (time)	Yield (%)[b] **3aA**
1	$Pd(OAc)_2$ (10)	dppf (10)	2	T (12 h)	62
2	$Pd(OAc)_2$ (20)	dppf (20)	2	T (11 h)	60
3	$Pd(OAc)_2$ (10)	PCy_3 (10)	2	T (14 h)	36
4	$Pd(dppf)Cl_2$ (10)	-	2	T (14 h)	66
5	$PdCl_2$ (10)	dppf (10)	2	T (14 h)	48
6	$PdCl_2$ (10)	PCy_3 (10)	2	T (16 h)	30
7	$Pd(OAc)_2$ (10)	dppf (10)	2	µW (15 min)	95
8	$Pd(OAc)_2$ (5)	dppf (5)	2	µW (15 min)	94
9	$Pd(OAc)_2$ (5)	dppf (5)	1	µW (15 min)	95
10	$Pd(dppf)Cl_2$ (5)	-	1	µW (20 min)	85
11[c]	$Pd(OAc)_2$ (5)	dppf (5)	1	µW (15 min)	90
12[d]	$Pd(OAc)_2$ (5)	dppf (5)	1	µW (15 min)	65

[a] All reactions were performed using 100 mg (0.34 mmol) of **1a** and 61µl (0.52 mmol) of *tert*-butyl isocyanide **(2A)**, PhMe (2.0 mL); [b]Isolated yields of chromatographically pure product; [c] DMF as medium; [d] DMSO as medium. T = thermal heating

resulted in inferior yield of **3aA** (entries 2-3). Testing the reaction with different palladium source also did not improve the yield (entries 4-6). Next the reaction in the presence of 10% $Pd(OAc)_2$, 10% dppf and 2.0 equiv of Cs_2CO_3 was probed under heating at 110 °C via microwave irradiation instead of conventional heating. It was gratifying to discover that the reaction was completed in 15 min and the yield of the product improved to 95% (entry 8). Subsequently we found that the reaction was successful even in the presence of 5 mol% of $Pd(OAc)_2$, 5 mol% of dppf and 1.0 equiv of Cs_2CO_3 without compromising the yield of **3aA** (entry 9). Use of 5 mol% of $Pd(dppf)Cl_2$ under identical condition gave **3aA** in 85% yield (entry 10). Further the reaction failed to furnish the product in the absence of a ligand or palladium source. Moreover, we found that replacing bromine with iodine in 1-(2-bromophenyl)-3-phenylurea afforded **3aA** in comparable yields. We also screened the reaction under DMF and DMSO as medium and found that the yield of **3aA** was comparable in DMF but inferior when DMSO was employed. However as compared to DMF, the work up of the reaction mixture in toluene was straightforward. Thus the reaction condition that worked best in our hands was 1.0 equiv of 2-bromphenylurea, 1.5 equiv of isonitrile, 5 mol% of $Pd(OAc)_2$, 5 mol% of dppf and 1.0 equiv of Cs_2CO_3 in toluene at 110 °C under microwave irradiation.

In the next stage we tested the scope of the developed protocol with respect to the 2-bromophenylurea and isonitrile and the results are presented in Fig. 2. Initially several 2-bromophenylureas were readily prepared by treating 2-bromoaniline with aryl or alkylisocyanates in methylene chloride in the presence of triethylamine. In the first set of reactions 2-bromophenylureas **(1b-i)** were treated with *tert*-butyl isonitrile **(2A)** to furnish the respective 4-(*tert*-butylimino)-*N*-substitutedphenyl or *N*-substitutedalkyl-4*H*-benzo[*d*][1,3]oxazin-2-amines **3bA-3iA** in excellent yields. Next set of reactions was

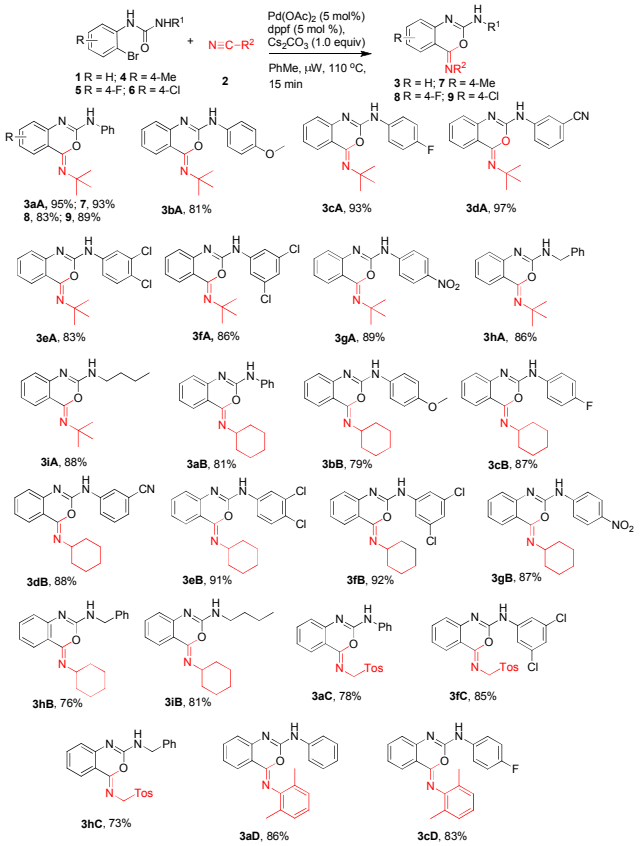


Fig. 2 Scope of the synthesis of *4H*-benzo[*d*][1,3]oxazin-2-amines

performed with 2-bromophenylureas **(1a-i)** and cyclohexylisonitrile **(2B)** leading to the synthesis of the products **(3aB,3cB-3iB)**. We discovered that the reaction between **1b** and **2B** did not result in the expected product under the optimized conditions. Fortunately however, altering the palladium source to $Pd(dppf)Cl_2$ gave the corresponding product **3bB** in 79% yield. But we were unable to assign a reason for this anomaly. The protocol was also probed with other isonitriles including 2,6-dimethylphenylisonitrile **(2C)** and tosylmethylisonitrile **(2D)** to furnish the corresponding products **3aC**, **3cC** and **3aD, 3fC** and **3hC** in good yields. To enhance the scope of the method, next the reaction was investigated with 2-bromophenylureas **(4-6)** bearing substitutions on the phenyl ring and it was observed that these substrates readily afforded the oxazine-2-amines **7-9**, respectively in 83-93% yields.

It is proposed that the reaction proceeds via a mechanism which is identical to the one reported by us earlier (Fig. 3).[1] In the first step halogen exchange with palladium would offer a Pd(II) intermediate species which is expected to undergo the isonitrile insertion resulting in an imidoyl derivative **II**. Subsequent deprotonation of the oxamidine **II** would result in a seven-member transition state **III**. The 4-imino-4*H*-benzo[*d*][1,3]oxazin-2-amine **3** would be formed by reductive elimination with regeneration of Pd(0) catalyst concurrently.(Fig. 3).

It is worth mentioning that during the course of this work Sharma and Jain reported a ligand-free palladium-assisted

insertion of isocyanide to urea derivative for cascade synthesis of phenylamino-substituted quinazolinones.[12] The mechanistic details proposed by these authors indicated that the initially formed benzoxazine species during the reaction undergoes a base mediated Mazurciewitcz-Ganesan type rearrangement to yield the quinazoline. Unfortunately, lack of key physical attributes (color and melting points) and chemical analyses or HRMS data of the isolated quinazolines in their report resulted in ambiguity, and therefore we considered reinvestigating the reaction. Performing the reaction in the absence of ligand in DMF or toluene however did not produce quinazoline in our hands as reported.

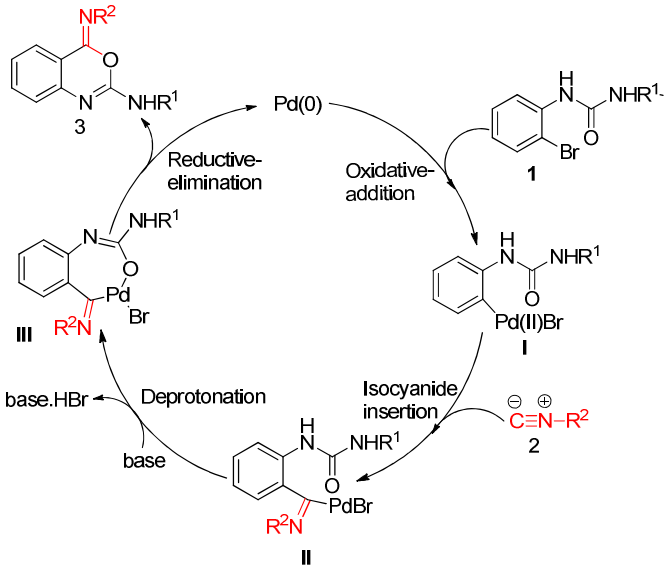
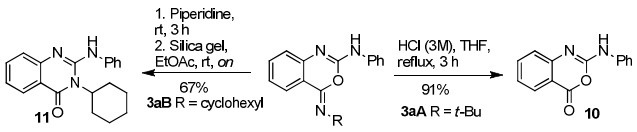


Fig. 3. Plausible mechanism for the formation of 4-imino-4*H*-benzo[*d*][1,3]oxazin-2-amines

Finally in pilot experiments we tested the utility of 4-(substitutedimino)-*N*-substituted-4*H*-benzo[*d*][1,3]oxazin-2-amines for preparing 2-aminobenzoxazin-4-one and 2-(substitutedamino)quinazolin-4(3*H*)-one following the literature procedures.[13-14] Initially compound **3aA** was treated with HCl (3M) in THF as medium under heating at reflux for 3 h to afford 2-(phenylamino)-4*H*-benzo[*d*][1,3]oxazin-4-one **(10)** in 91% yield (Scheme 1). In other reaction compound **3aB** was treated with neat piperidine at room temperature for 3 h followed by addition of silica gel and leaving the reaction overnight. This resulted in transformation of **3aB** to the quinazolin-4(3*H*)-one **11** in 67% yield.



Scheme 1 Transformations of 4-(substitutedimino)-*N*-substituted-4*H*-benzo[*d*][1,3]oxazin-2-amines to 2-aminobenzoxazin-4-one and 2-(substitutedamino)quinazolin-4(3*H*)-one

Conclusions

In summary, we have demonstrated the microwave-assisted palladium-catalysed isonitrile insertion into 2-bromophenylureas for an efficient synthesis of 4-substituted imino *4H*-benzo[*d*][1,3]oxazin-2-amines. The scope of the methodology accommodates all types of 2-halophenylureas (aromatic and aliphatic) and the commercially available isonitriles. The use of microwave allows the reaction to be completed in very short span of time. The products generated during the study are demonstrated to be viable precursor for accessing 2-aminobenzoxazin-4-ones and 2-(substitutedamino)quinazolin-4(3*H*)-ones.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [Experimental protocols, spectroscopic details and copies of ^{1}H and ^{13}C-NMR spectra of all the compounds are included]. See DOI: 10.1039/b000000x/

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