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Palladium-Catalyzed Synthesis of 4-Aminophthalazin-1(2*H*)-ones by Isocyanide Insertion

Tjøstil Vlaar,[†] Eelco Ruijter,*[,†] Anass Znabet,[†] Elwin Janssen,[†] Frans J. J. de Kanter,[†] Bert U. W. Maes,[§] and Romano V. A. Orru*[,†]

Department of Chemistry & Pharmaceutical Sciences and Amsterdam Institute for Molecules, Medicines and Systems (AIMMS), VU University Amsterdam, De Boelelaan 1083, 1081 HV Amsterdam, The Netherlands, and Organic Synthesis, Department of Chemistry, University of Antwerp, Groenenborgerlaan 171, B-2020 Antwerp, Belgium

r.v.a.orru@vu.nl; e.ruijter@vu.nl

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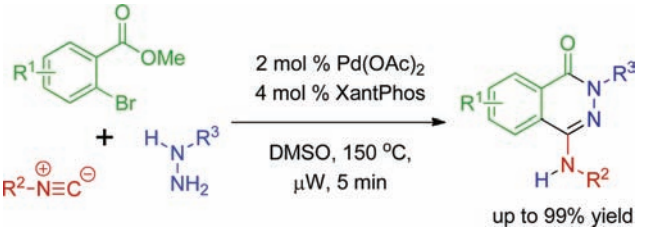
ABSTRACT



Palladium-catalyzed cross-coupling of a wide range of substituted *o*-(pseudo)halobenzoates and hydrazines with isocyanide insertion followed by lactamization efficiently affords 4-aminophthalazin-1(2*H*)-ones that are difficult to obtain regioselectively by classical methods.

Efficient access to libraries of functionalized heterocycles for lead discovery and optimization is essential for drug development and relies heavily on combinatorial chemistry and high-speed synthesis. In this respect, multicomponent reactions (MCRs)[1] are valuable tools, since they allow rapid generation of complex and structurally diverse heterocycles.[2] 4-Aminophthalazin-1(2*H*)-ones (APOs, **2**) are exceptional and structurally interesting heteroaromatics[3] that have shown potential as anticancer agents[4] and in the treatment of autoimmune and inflammatory diseases.[5] In addition, they have been identified as PARP inhibitors.[6] Very recently, 2-phenyl APOs have been reported as a decorable scaffold for the design of human A3 adenosine receptor antagonists.[7] Vatalanib (Scheme 1), a promising drug candidate in clinical trials for the treatment of several types of cancer,[8] can be prepared from APOs. Despite this promising precedence, APOs have only scarcely been studied, which might be explained by the tedious linear synthesis starting from

[†] VU University Amsterdam.
[§] University of Antwerp.

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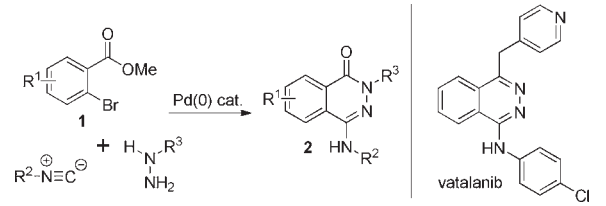
phthalic anhydride.[4,7] Furthermore, nonsymmetric substitution of the phenyl ring is difficult due to formation of regioisomers, severely limiting structure–activity relationship (SAR) studies of APOs and related heteroaromatics. Additionally, bulky amino groups are difficult to introduce due to low nucleophilicity.

Scheme 1. MCR Approach toward 4-Aminophthalazinones



Palladium-catalyzed iminoacylation by isocyanide insertion is an efficient but relatively unexplored method that offers significant advantages over the well-known carbon monoxide insertions,[9] such as an additional diversity point for scaffold decoration and more practical handling.[10] It is therefore not surprising that interest in this field has increased significantly recently.[11] In light of our interest in employing iminoacylation in palladium-catalyzed cascade reactions,[12,13] we envisioned an MCR approach toward APOs starting from *o*-bromobenzoates (**1**), isocyanides, and hydrazines (Scheme 1). Hydrazine is a challenging coupling partner and has only very recently successfully been used in the Buchwald–Hartwig reaction.[14] We started our investigations using methyl *o*-bromobenzoate (**1a**), *tert*-butyl isocyanide, and hydrazine monohydrate as a benchmark reaction using $Pd(OAc)_2$ (10 mol %) and XPhos (20 mol %), as the catalytic system, in DMF with KOAc as the base,[13] which did not result in any product formation under conventional heating. Initial screenings indicated that employing hydrazine as both a reagent and a convenient and cheap base under microwave irradiation did furnish **2a** in 30% yield (Table 1, entry 1). We were pleased to find that dppf is a much better ligand than XPhos (entry 2), providing the product in 55% yield with only 2 mol % of $Pd(OAc)_2$ (entry 3). Lowering the palladium/ligand ratio to 1:1.1 reduced the yield significantly (entry 4). Several ligands were screened (entries 5–7), indicating that bidentate ligands are essential, and XantPhos is especially effective. A negative control experiment validated that a palladium catalyst is required (entry 8). DMSO proved to be a highly effective solvent, affording the product in quantitative yield (entry 13). The reaction was equally efficient when the reaction time was reduced to just 5 min (entry 14). Microwave irradiation proved clearly superior to conventional heating (entry 15, preheated oil bath).[15,16]

After having defined the optimal catalytic system and reaction conditions, we explored the scope of the reaction (Scheme 2). In addition to aryl bromides, also aryl iodides and triflates provided product **2a** in excellent yields. Aryl chlorides, however, proved to be less efficient coupling partners. Both electron-donating and -withdrawing substituents are tolerated on the aryl bromide (**2b–d**), although a 5-nitro group did not provide an isolable amount of product. The amino-substituted substrate **1c** was not fully consumed under the reaction conditions, and the remaining starting material could be isolated. In the case of the chloro-substituted substrate **1d**, a more complex reaction mixture was observed, presumably due to the competing oxidative addition of the aryl chloride bond. Products **2c** and **2d** are noteworthy, since they allow easy subsequent modifications to increase molecular diversity. C5- and C6-substituted APOs (**2e**, **2f**) as well as a naphthalene-fused derivative (**2g**) were obtained in excellent to quantitative yields. The use of substituted hydrazines, however, proved to be less straightforward. Replacing hydrazine monohydrate with phenylhydrazine under the standard conditions did not lead to product formation. We argued that, since hydrazine is both a reagent and base in this reaction, the difference in basicity might be responsible for the observed results. Accordingly, we examined the use of an additional base and were delighted to observe product formation using triethylamine as the base. After optimization we obtained **2h** in 63% yield using $i\mathrm{Pr}_2\mathrm{NH}$ (3 equiv).[16] Substitution on the methyl benzoate is still tolerated (**2i**, **2j**), although a strongly electron-donating methoxy group in the *ortho* position decreases the yield. Interestingly, a change in the electronic character of the aryl hydrazine has a pronounced effect. Electron-poor *para*-trifluoromethylphenylhydrazine gives **2k** in 37% yield, whereas *para*-methoxyphenylhydrazine gave only trace amounts of product. Methylhydrazine can be used, but product **2l** was obtained in poor yield (30%). These *N*-alkylated and *N*-arylated APOs can alternatively be obtained from the corresponding *N*-unsubstituted APOs.[3]

The substrate tolerance of the isocyanide was examined next, which unfortunately revealed that the reaction is

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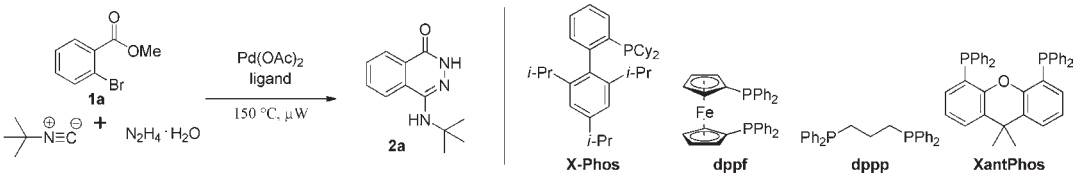
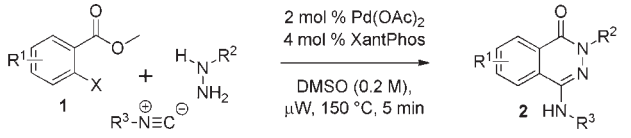
Table 1. Optimization of the Palladium-Catalyzed MCR toward 4-Aminophthalazin-1(2*H*)-ones[a]

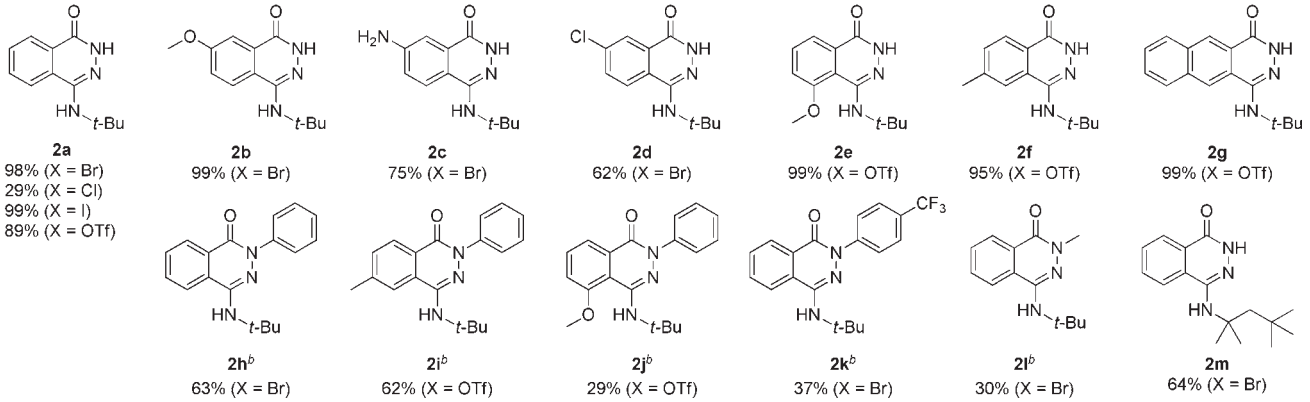


entry	solvent	ligand	Pd (mol %)	Pd/L ratio	time (min)	conversion (%)[b]	yield (%)[b]
1	DMF	X-Phos	10	1:2	20	>99%	30%
2	DMF	dppf	10	1:2	20	>99%	81%
3	DMF	dppf	2	1:2	20	>99%	55%
4	DMF	dppf	2	1:1.1	20	>99%	31%
5	DMF	PPh_3	2	1:2	20	41%	5%
6	DMF	dppp	2	1:2	20	70%	21%
7	DMF	XantPhos	2	1:2	20	>99%	64%
8	DMF	–	0	–	20	39%	0%
9	MeCN	XantPhos	2	1:2	20	50%	31%
10	PhMe	XantPhos	2	1:2	20	23%	2%
11	THF	XantPhos	2	1:2	20	23%	5%
12	NMP	XantPhos	2	1:2	20	58%	40%
13	DMSO	XantPhos	2	1:2	20	>99%	100%
14	**DMSO**	**XantPhos**	**2**	**1:2**	**5**	**>99%**	**99%**
15[c]	DMSO	XantPhos	2	1:2	5	86%	78%

[a] Standard reaction conditions: $Pd(OAc)_2$, ligand, methyl *o*-bromobenzoate (**1a**, 0.50 mmol), *tert*-butyl isocyanide (0.75 mmol), hydrazine monohydrate (1.05 mmol), 2.5 mL indicated solvent, microwave irradiation at 150 °C. [b] Conversion of methyl *o*-bromobenzoate, determined by GC analysis using dodecane as an internal standard. [c] Conventional heating (oil bath). DMF = *N,N*-dimethylformamide, THF = tetrahydrofuran, NMP = *N*-methylpyrrolidone, DMSO = dimethylsulfoxide.

Scheme 2. Substrate Scope of the Palladium-Catalyzed MCR toward 4-Aminophthalazin-1(2*H*)-ones[a]



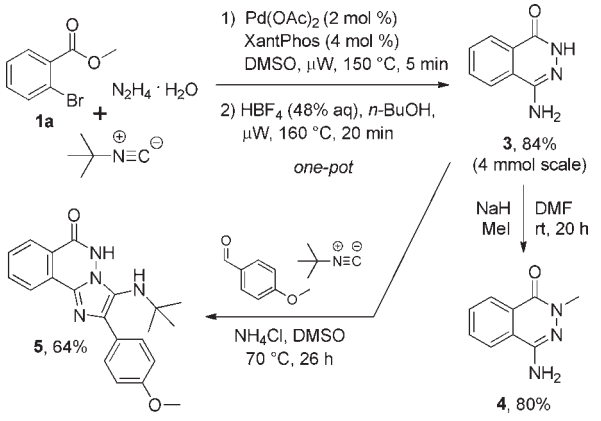


[a] Conditions: ArX (0.50 mmol), isocyanide (0.75 mmol), hydrazine monohydrate (1.05 mmol), $Pd(OAc)_2$ (2 mol %), XantPhos (4 mol %) in DMSO (2.5 mL), 5 min at 150 °C (μW). Yields refer to isolated products. [b] Conditions as under *a*, but using a substituted hydrazine (1.25 mmol) and *i*-Pr_2NH (1.5 mmol).

highly specific for tertiary alkyl isocyanides. Although Walborsky's reagent provided product **2m** in 64% yield, neither primary and secondary aliphatic nor aromatic isocyanides gave the desired product. We do not yet have

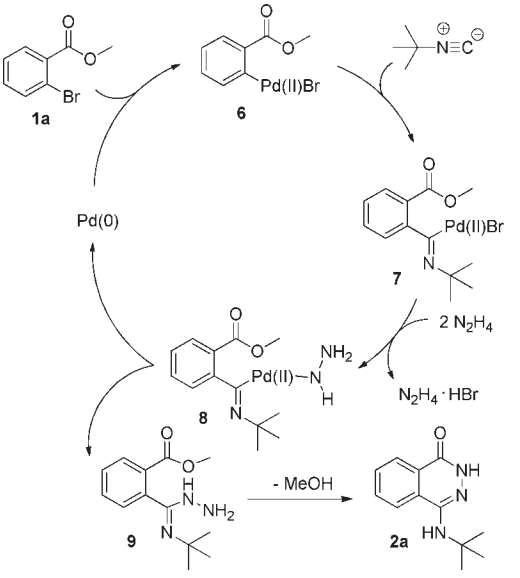
a satisfactory explanation for this high sensitivity. A possibility could be the tendency for less bulky isocyanides to form stable fully ligated palladium complexes, thereby inhibiting catalysis.[17] Fortunately, the *tert*-butyl group is easily removed in a one-pot procedure using Guchhait's conditions,[18] although a solvent switch is required (Scheme 3). The unprotected amine **3** is isolated in a very good yield (84%) at a 4 mmol scale and can subsequently serve as a platform for diversification. Accordingly, we selectively N2-alkylated amine **3** to obtain the methylated product **4** (80% yield), which can easily be further modified.[7] In addition, we used amine **3** in a Groebke–Blackburn–Bienaymé MCR,[19] providing imidazo[2,1*a*]-phthalazin-6-one **5** in 64% yield (54% over two steps from commercially available starting materials). The imidazo-[2,1*a*]phthalazin-6-one scaffold is virtually unexplored, and only one simple example has been reported in the literature so far.[20]

Scheme 3. One-Pot MCR/Dealkylation Strategy and Subsequent Diversification of **3**



A plausible mechanism for the three-component reaction toward APOs is depicted in Scheme 4. Oxidative addition of **1a** to the Pd(0) catalyst followed by isocyanide insertion leads to palladium species **7**. Coordination of hydrazine to Pd(II) and subsequent deprotonation followed by reductive elimination provides product **9**, which cyclizes and tautomerizes under the reaction conditions to form product **2a**. Alternatively, hydrazide formation by hydrazinolysis of the ester functional group may occur first. This is, however, not in accordance with the observed reaction products when phenylhydrazines are used as reactants. Furthermore, only trace amounts of the hydrazide are formed in the absence of a palladium catalyst (Table 1, entry 8). It is therefore highly unlikely that hydrazide formation occurs prior to the isocyanide insertion reaction.

Scheme 4. Proposed Mechanism of the Reaction (ligands on Pd are omitted for clarity)



In summary, we have developed a fast and efficient palladium-catalyzed MCR toward 4-aminophthalazin-1(2*H*)-ones that (unlike existing methods) allows the straightforward regioselective introduction of substituents on the phenyl ring. Our method represents the first example of a multicomponent reaction combining isocyanides and free hydrazines as well as one of the few palladium-catalyzed reactions using hydrazines as reactants. Although the scope with regard to the hydrazine and isocyanide inputs is limited, a simple one-pot dealkylation strategy provides the unprotected APOs in excellent yields. Subsequent complexity-generating reactions then allow the construction of functionalized APOs as well as new molecular scaffolds in a more time- and step-efficient manner than conventional procedures.

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

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