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Microwave-Assisted Sequential Amide Bond Formation and Intramolecular Amidation: A Rapid Entry to Functionalized Oxindoles

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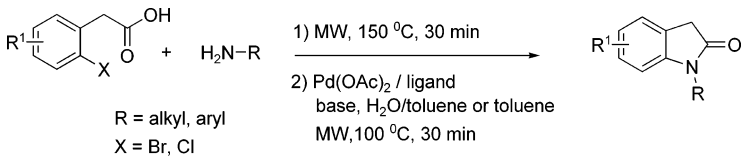
ABSTRACT



A general method has been developed for the synthesis of N-substituted oxindoles. The two-step process involves initial microwave-assisted amide bond formation between 2-halo-arylacetic acids and various alkylamines and anilines, followed by a palladium-catalyzed intramolecular amidation under aqueous conditions. In the case of alkylamines, the procedure can be carried out as a one-pot process without isolation of the intermediate amide.

The indole template is generally recognized as a privileged structure in medicinal chemistry, and in particular, oxindoles are important constituents of natural indole alkaloids as well as drugs in development and also in the clinic.[1] In this context, it is important to continue to develop efficient methods for the synthesis of this class of compounds, especially routes based upon readily available starting materials. Although a number of transition-metal-catalyzed[2] and radical-mediated[3] reactions have been reported for the synthesis of oxindoles, there remains a need for new methods.

A conceptually different approach to the construction of heterocycles, including oxindoles, has arisen from the work of Buchwald, Hartwig, and others and is based upon palladium-catalyzed intramolecular amination/amidation/Heck reaction of appropriately substituted arenes, via C−N/C−C bond formation.[4] A recent report describes the use of nickel rather than palladium.[5]

In parallel with these developments in the metal-mediated construction of C−C and C−N bonds, there has been a general recognition that microwave heating can accelerate a broad range of reactions in organic synthesis, especially in the field of metal-catalyzed cross-coupling reactions.[6] Mi-

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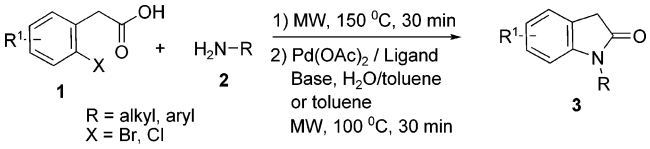
crowave heating can dramatically reduce reaction times, increase product purity and yields, and allow precise control of reaction parameters, all of which are crucial factors to consider when developing reaction protocols for both routine synthetic transformations and parallel synthesis. Herein, we present an efficient approach to substituted oxindoles using microwave-assisted amide bond formation followed by palladium-catalyzed intramolecular amidation reaction as shown in Scheme 1.

Scheme 1. Synthesis of Substituted Oxindoles



Our approach was inspired by previous studies by Buchwald et al., who reported the palladium-catalyzed intramolecular amination and amidation of aryl bromides for the synthesis of five-, six-, and seven-membered rings.[7] They described the synthesis of N-substituted oxindoles, from the corresponding 2-bromo-N-substituted phenylacetamides, using palladium acetate and various phosphine ligands in high yields and with reaction times of 24−36 h. We envisaged an alternative approach involving initial generation of the amide by microwave-assisted coupling of a 2-haloarylacetic acid **1** with an amine **2**, followed by palladium-catalyzed intramolecular amidation to yield **3**. Since the initial amide-forming reaction generates a molar equivalent of water, it was essential to identify conditions in the second step that were tolerant of water.

Heating a mixture of 2-bromophenylacetic acid **4** and benzylamine **5** under solvent-free MW conditions led to rapid (ca. 30 min) formation of the corresponding amide in good to excellent yield.[8] To identify optimal conditions for the palladium-catalyzed intramolecular amidation reaction to give **6**, we screened a range of different phosphine ligands **7**−**11** (Figure 1) for activity using various combinations of palladium source/solvent/base (Table 1). In general, the best results were obtained using either ligand **10** or **11** (6 mol %) in the presence sodium hydroxide or cesium carbonate (2.0 equiv).

These optimized conditions were then applied to the synthesis of a range of substituted oxindoles as shown in Table 2. In the case of the alkylamines, the palladium-catalyzed intramolecular amidation step was carried out without prior isolation of the intermediate amide. The reaction mixture was simply purged with nitrogen gas prior

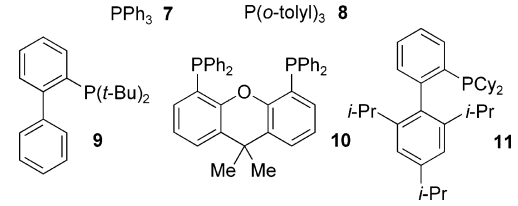


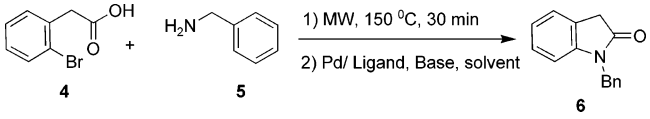
Figure 1. Ligands screened for intramolecular amidation.

to introduction of the reagents for the second step. For anilines it was necessary to work-up the reaction by extraction into chloroform, followed by an aqueous wash and evaporation of the organic layer to give a crude product that was used directly for the next step.

The intramolecular amidation reactions were generally complete within 30 min, and with only a few exceptions (entries 14, 15, 19, and 22) the yields for the two steps were excellent, typically greater than 80%. Scheme 2 shows the potential further application of the derived oxindoles in which the product **12** from entry 22 was subjected to a microwave-assisted palladium-catalyzed bis-amination reaction with 3-fluoroaniline to give the new N-substituted oxindole **13** in 65% yield.

A number of features of the procedure described above deserve comment: (i) the intramolecular amidation reaction proceeds well under partially aqueous conditions, in the case of alkylamines, and is subject to substantial acceleration in rate when conducted with microwave heating; (ii) good yields were obtained without the use of phase-transfer reagents, which have been used previously for intramolecular amina-

Table 1. Optimization of Reaction Conditions[a]



entry	conditions	yield[b] (%)
1	$Pd(PPh_3)_4$, NaO*t*-Bu, toluene	nd
2	$Pd(PPh_3)_4$, K_2CO_3, dioxane	10
3	POPd,[c] K_2CO_3, toluene	15
4	$Pd(OAc)_2$, **7**, NaO*t*-Bu, toluene	nd
5	$Pd(OAc)_2$, **8**, Cs_2CO_3, toluene	58
6	$Pd(dba)_3$, **8**, K_2CO_3, tolune	55
7	$Pd(OAc)_2$, **9**, H_2O/toluene	60
8	$Pd(OAc)_2$, **10**, Cs_2CO_3, toluene	78
9	$Pd(dba)_3$, **10**, Cs_2CO_3, toluene	65
10	$Pd(OAc)_2$, **10**, NaOH, H_2O/toluene	82
11	$Pd(OAc)_2$, **10**, NaOH, H_2O/DME	nd
12	$Pd(OAc)_2$, **11**, Cs_2CO_3, toluene	92
13	$Pd_2(dba)_3$, **11**, Cs_2CO_3, toluene	89
14	$Pd(OAc)_2$, **11**, NaOH, H_2O/toluene	95

[a] Reaction was conducted with 3 mol % catalyst, 6 mol % ligand, 1.0 equiv of 2-bromophenyl acetic acid, and 2.0 equiv of base for 30 min at 100 °C on a 1.0 mmol scale of acid. [b] Isolated yields. [c] POPd: $PdCl_2[(t\text{-}Bu)_2P(OH)]_2$, purchased from Combiphos Catalysts, Inc.

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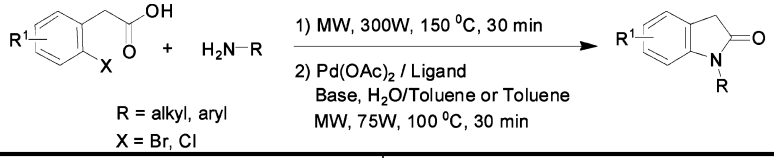
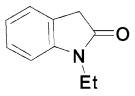
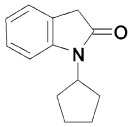
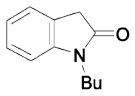
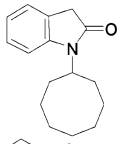
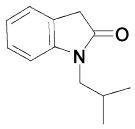
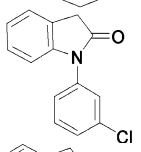
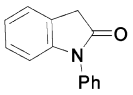
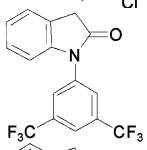
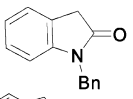
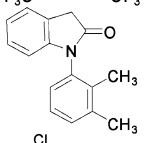
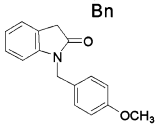
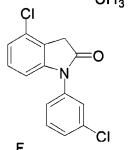
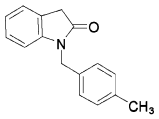
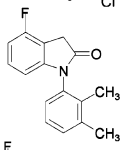
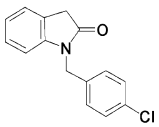
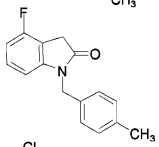
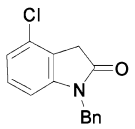
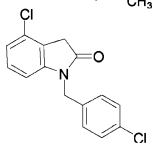
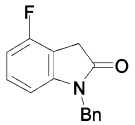
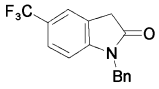
Table 2. Microwave-Assisted Synthesis of Substituted Oxindoles[a]

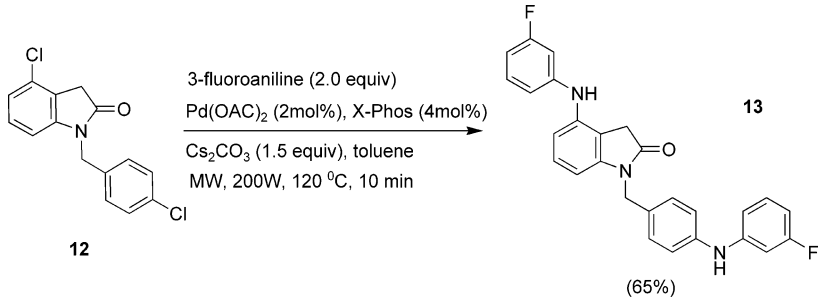


entry	acid	amine	product	yield[b] (%)	entry	acid	amine	product	yield[b] (%)
1 2	2-bromo 2-chloro	Et-NH_2		92 85	14	2-bromo	cyclopentyl amine		50
3	2-bromo	Bu-NH_2		89	15	2-bromo	cycloctyl amine		30
4	2-bromo	^{i}Bu-NH_2		85	16[c]	2-bromo	3-chloro-aniline		80
5[c] 6[c]	2-bromo 2-chloro	Ph-NH_2		82 80	17[c]	2-bromo	3,5-CF_3-aniline		72
7 8	2-bromo 2-chloro	Bn-NH_2		95 90	18[c]	2-bromo	2,3-dimethyl-aniline		80
9	2-bromo	*p*-methoxy benzylamine		92	19[c]	2,6-dichloro	3-Cl-aniline		45
10	2-bromo	*p*-methyl benzylamine		85	20[c]	2-chloro, 6-fluoro	2,3-dimethyl-aniline		82
11	2-bromo	*p*-chloro benzylamine		70	21	2-chloro, 6-fluoro	*p*-methyl benzylamine		90
12	2,6-dichloro	Bn-NH_2		80	22	2,6-dichloro	*p*-chloro-benzylamine		54
13	2-chloro, 6-fluoro	Bn-NH_2		96	23	2-chloro-5-trifluoro	Bn-NH_2		93

[a] Reagents and conditions: acid (1.0 mmol), amine/aniline (1.0 mmol), MW 300W, 150 °C, 30 min then, $Pd(OAc)_2$ (3 mol %), ligand **11** (6 mol %), NaOH (2.0 equiv) H_2O/toluene (2 mL 1:1), microwave 75 W, 100 °C, 30 min. [b] Isolated yield based on amide. [c] Isolated amide (1.0 mmol), Cs_2CO_3 (1.5 equiv), toluene (2 mL), microwave 200 W, 100 °C, 30 min.

tion reactions;[9] (iii) the intramolecular amidation reaction can be carried out using *aryl chlorides* in addition to aryl bromides, thereby greatly extending the range of substrates that can be used; (iv) *anilines can be used*, in addition to alkylamines, extending the range of N-substituted oxindoles that can be prepared.

Scheme 2. Palladium-Catalyzed Intermolecular Amination



In conclusion, we have developed an efficient route to a range of N-substituted oxindoles using sequential microwave-assisted amide synthesis and intramolecular amidation reactions. The approach is particularly efficient when using alkylamines since there is no need to isolate the intermediate amide.

Acknowledgment. We are grateful to CEM Corporation, UK, for provision of a Discover microwave synthesizer.

Supporting Information Available: Experimental details and spectral data for all transformations and compounds described. This material is available free of charge via the Internet at http://pubs.acs.org.

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