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Rapid Access to Oxindoles by the Combined Use of an Ugi Four-Component Reaction and a Microwave-Assisted Intramolecular Buchwald–Hartwig Amidation Reaction

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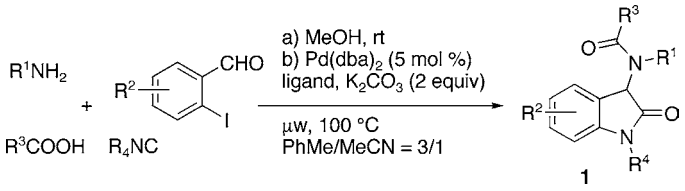
ABSTRACT



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A two-step sequence involving an Ugi four-component reaction (Ugi-4CR) and a palladium-catalyzed intramolecular amidation of aryl iodide has been developed for rapid access to functionalized oxindole (1). Microwave heating was used to accelerate and to improve the efficiency of the intramolecular Buchwald–Hartwig reaction.

The rapid generation of molecular complexity and diversity from simple and readily accessible starting materials is a contemporary research theme in the practice of modern organic synthesis.[1] In this context, the combination of a multicomponent reaction[2] with an efficient post-transformation, typically a ring-forming process, has been proven to be a powerful tool for the synthesis of highly functionalized heterocyclic compounds.[3] Indeed, being capable of combining three or more reactants together in a single ordered event, a multicomponent reaction, offers not only great molecular complexity and diversity per step but also the possibility of introducing matched functionalities suitable for further transformations. A variety of reactions including condensation,[4] ring-closure metathesis,[5] cycloaddition,[6] macrolacton-

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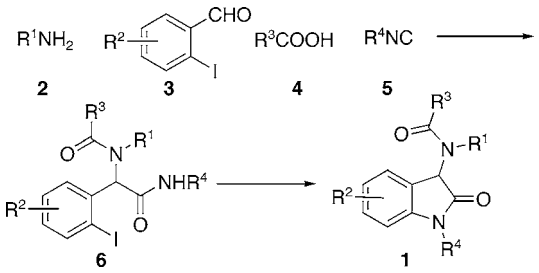
ization,[7] an intramolecular S_NAr reaction,[8] etc. have been combined with an isonitrile-based multicomponent reaction (MCR)[9] for the construction of cyclic scaffolds.

The palladium-catalyzed C−C bond and C-heteroatom bond-forming reactions have been developed into reliable and versatile synthetic methods. Association of these transformations with MCRs has naturally attracted the attention of synthetic chemists and has led to the development of several facile syntheses of medicinally relevant heterocycles.[10] We have recently reported a two-step synthesis of 1,4-benzodiazepine-2,5-diones and its tetracyclic derivatives by a sequence of an Ugi four-component reaction (Ugi-4CR) and a copper/palladium-catalyzed intramolecular N-arylation process.[11] As a logical extension of this work, we became interested in the synthesis of an oxindole (**1**) whose structure has been found in a vast number of natural products and pharmaceuticals.[12] The synthetic sequence that we envisaged is shown in Scheme 1. Thus, reaction of an amine (**2**), a

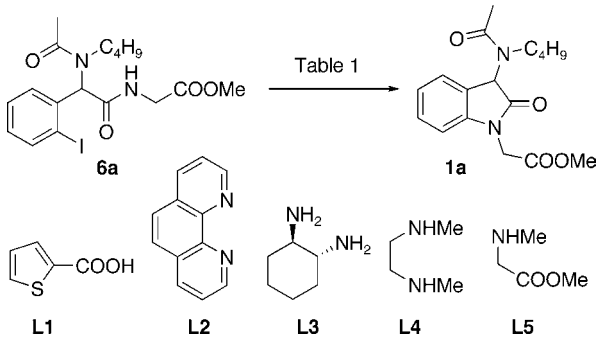
Scheme 1. Synthesis of Oxindole **1** by a Sequence of an Ugi-4CR and an Intramolecular N-Arylation Process



functionalized *ortho*-iodobenzaldehyde (**3**), a carboxylic acid (**4**), and an isonitrile (**5**) should provide α-acylaminophenylacetamide (**6**), which upon an intramolecular N-arylation under appropriate conditions should afford the desired oxindole (**1**). Very recently, Kalinski and co-workers reported the synthesis of **1** employing the same synthetic strategy.[13] However, the yield of cyclization remained low at best (4−45%). We report herein our own efforts that led to the development of a very efficient synthesis of oxindoles (**1**).

Amide (**6a**) was prepared in quantitative yield by reacting *n*-butylamine (**2a**), *ortho*-iodobenzaldehyde (**3a**), acetic acid (**4a**), and methyl α-isocyanoacetate (**5a**) under classic Ugi conditions (MeOH, rt). Cyclization of **6a** was initially examined under the influence of a copper catalyst (Table 1).[14,15] As can be seen, conditions previously optimized for

Table 1. Copper-Catalyzed Intramolecular Ullmann Reaction for the Synthesis of Oxindole: A Survey of Reaction Conditions[a]



entry	solvent	ligand	base	temp (°C)	yield
1	DMSO	**L1**	K_2CO_3	110	0%
2	DMSO	**L1**	Cs_2CO_3	90	0%
3	dioxane	**L1**	Cs_2CO_3	reflux	26%
4	dioxane	**L1**	K_3PO_4	reflux	30%
5	dioxane	**L1**	K_2CO_3	reflux	20%
6	toluene	**L1**	Cs_2CO_3	reflux	42%
7	toluene	**L1**	K_3PO_4	reflux	0%
8	toluene	**L1**	Cs_2CO_3	reflux	28%[b]
9	toluene	**L2**	Cs_2CO_3	reflux	14%
10	toluene	- - -	Cs_2CO_3	reflux	19%
11	toluene	**L3**	Cs_2CO_3	reflux	0%
12	toluene	**L4**	Cs_2CO_3	reflux	0%
13	toluene	**L5**	Cs_2CO_3	reflux	20%

[a] Unless specified, 0.2 equiv of CuI was used. [b] $CuCl_2$ was used.

the synthesis of benzodiazepinedione (CuI, thiophene-2-carboxylic acid **L1**, DMSO, K_2CO_3, 110 °C)[11] failed to catalyze the formation of oxindole, and thus a survey of reaction conditions was performed varying the solvents, the bases, and the ligands. As is seen, toluene turned out to be the solvent of choice whereas cesium carbonate gave results as a base superior to those for potassium carbonate and potassium phosphate. However, under the best conditions we found, the yield of **1a** did not exceed 42% (entry 6).

The moderate yield obtained on the copper-catalyzed cyclization of **6a** prompted us to examine the palladium-catalyzed version using **6b** as a test substrate (Table 2).[16] Although cyclization of *o*-bromophenylacetamide is well-

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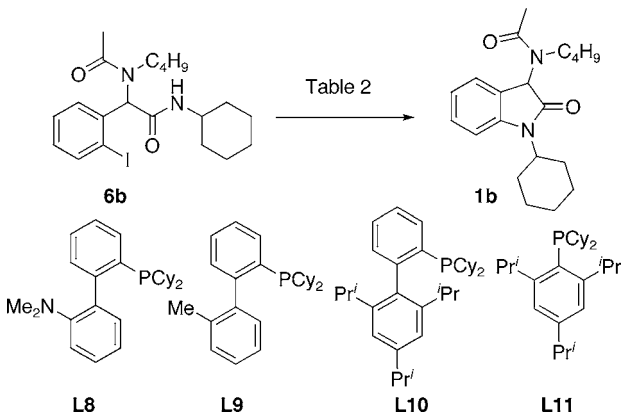
Table 2. Palladium-Catalyzed Intramolecular Buchwald–Hartwig Reaction: A Survey of Reaction Conditions[a]



entry	solvent	Pd	ligand	temp (°C)	time (h)	yield[f]
1	PhMe	$Pd(dba)_2$	BINAP	100	24	<20%
2	PhMe	$Pd(OAc)_2$	MOP	100	24	50%
3	PhMe	$Pd(OAc)_2$	MOP	μW[b]	1	0%
4	S[c]	$Pd(OAc)_2$	MOP	μW[b]	1	0%
5	S[c]	$Pd(dba)_2$	MOP	μW[b]	1	71%
6	S[d]	$Pd(dba)_2$	MOP	μW[b]	1	80%
7	S[e]	$Pd(dba)_2$	**L8**	μW[b]	2	61%
8	S[e]	$Pd(dba)_2$	**L9**	μW[b]	1.5	82%
9	S[e]	$Pd(dba)_2$	**L10**	μW[b]	2	48%
10	S[e]	$Pd(dba)_2$	**L11**	μW[b]	2	24%
11	S[c]	$Pd(dba)_2$	**L9**	μW[b]	1.5	82%

[a] General conditions: 5 mol % of Pd, 5 mol % of ligand, 2 equiv of K_2CO_3. [b] Microwave heating with a Discover microwave reactor from CEM. Irradiation power: 180 W. Ramp time: 1 min. 100 °C. [c] PhMe/MeCN = 1:1. [d] PhMe/MeCN = 3:1. [e] PhMe/MeCN = 2:1. [f] Yield refers to isolated yield.

known,[17] initial experiments using BINAP (**L6**) as a ligand and $Pd(dba)_2$ as a palladium source afforded the desired

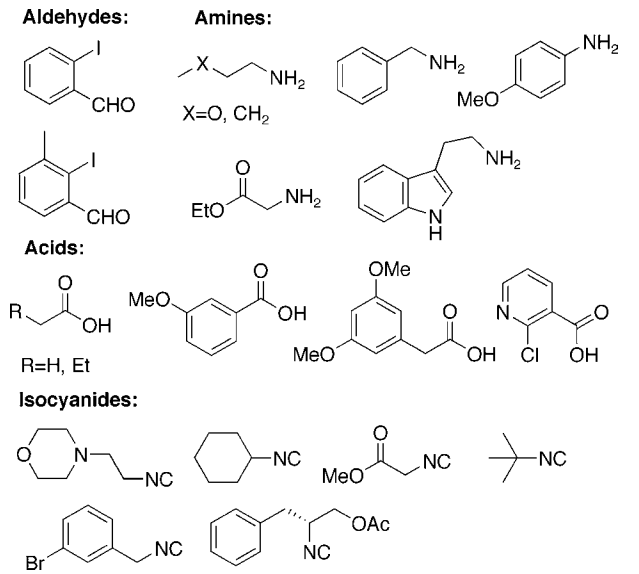


Figure 1. Starting materials for an Ugi-4CR.

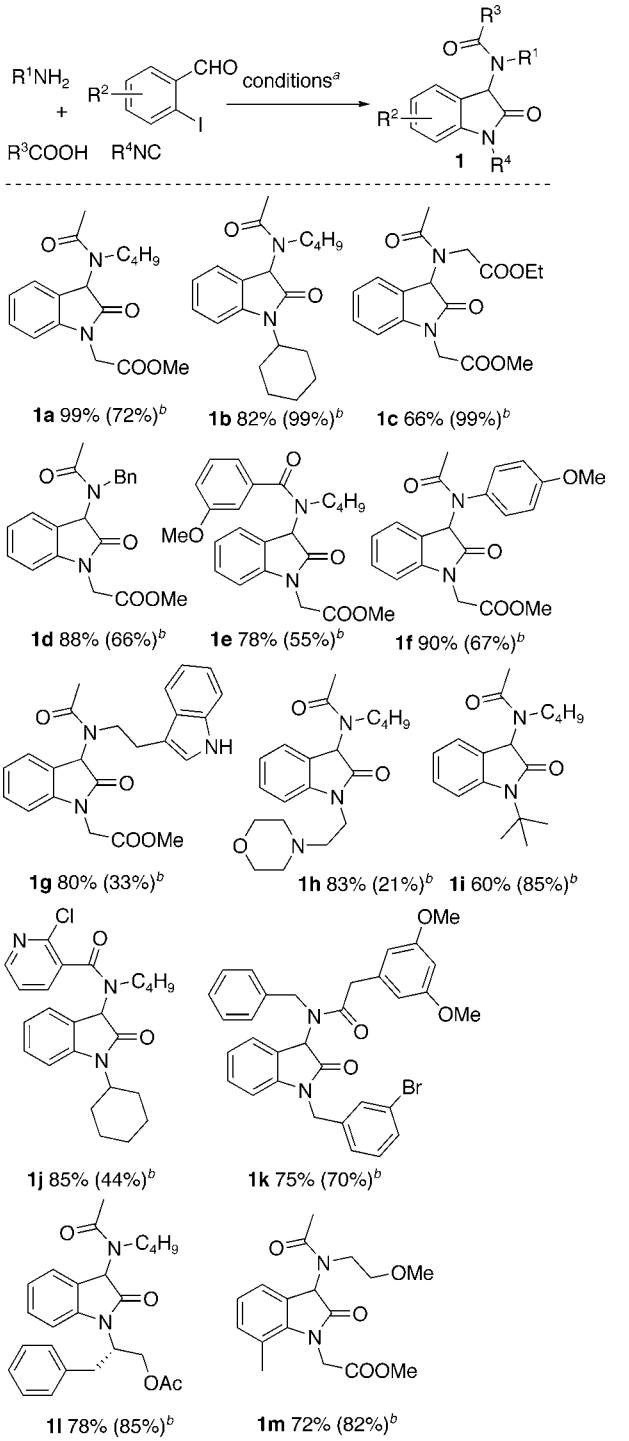


Figure 2. Synthesis of oxindoles by a sequence of an Ugi-4CR/intramolecular Buchwald–Hartwig reaction.[a] [a]Conditions: (i) MeOH, rt; (ii) $Pd(dba)_2$ (5 mol %), Me-Phos, K_2CO_3 (2 equiv), μW, 100 °C, PhMe/MeCN = 3:1, reaction time 1–2.5 h. [b]Yield of an Ugi-4CR.

oxindole **1b** in low yield (entry 1). Up to 50% yield of **1b** was obtained when the reaction was catalyzed by $Pd(OAc)_2$ in the presence of a monophosphine ligand (MOP, **L7**) (entry 2). The controlled microwave heating technique was next applied with the hope to increase the cyclization efficiency

(Table 1).[18,19] Interestingly, applying microwave heating under otherwise identical conditions, we observed no cyclization in toluene (entry 3) and toluene−MeCN (entry 4). However, by simply switching from $Pd(OAc)_2$ to $Pd(dba)_2$, cyclization of **1b** occurred smoothly to provide **1b** in 80% yield. We have also briefly examined the effect of ligand structure on the reaction efficiency and found that Me-Phos (**L9**) furnished results superior to those for Davephos (**L8**), X-phos (**L10**), and dicyclohexyl(2,4,6-triisopropylphenyl) phosphine (**L11**). Overall, under optimized conditions [5 mol % of $Pd(dba)_2$, 5 mol % of Me-Phos, K_2CO_3, tol-MeCN = 3:1, μW, 100 °C], cyclization of **6b** provided **1b** in 82% yield (entries 8 and 11).

The optimized conditions were then applied to the synthesis of a range of oxindoles in combination with the Ugi reaction. From two aldehydes, six amines, five carboxylic acids, and six isonitriles (Figure 1), the oxindoles synthesized were listed in Figure 2. As is seen, a range of functional groups such as ester, amine, ether, heterocyclic nuclei such as pyridine (**1j**), and indole (**1g**) are tolerated. Sterically hindered amides such as tertiary butylamide are readily cyclized to give the corresponding oxindole (**1i**) in 60% yield. The reaction is not sensitive to steric hindrance around the iodide because the 7-methyloxindole (**1m**) can be prepared in good yield (72%). Cyclization of **6j** (Figure 3) is chemoselective leading to the formation of the desired oxindole (**1j**) in 85% yield without touching the aryl chloride function, which could in principle be further functionalized by taking advantage of the transition-metal-catalyzed transformation of aryl chlorides.[20] Interestingly, even aryl bromide was tolerated as evidenced by the formation of compound **1k** in 75% yield. When Ugi adduct **6f** (Figure 3) was subjected to the present N-arylation conditions, only oxindole **1f** was isolated; the dihydrophenanthridine (**7**) resulting from the potentially competitive C−H activation process was not observed.[21]

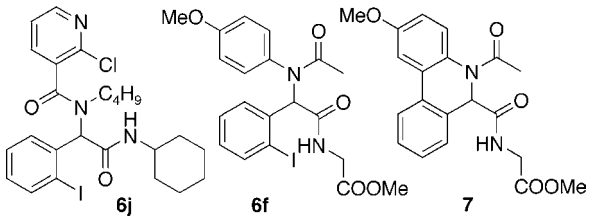


Figure 3. Structure of Ugi adducts and a possible side product.

Finally, cyclization of **6a** (cf. Table 1) took place in the absence of microwave irradiation under otherwise identical conditions [$Pd(dba)_2$ (5 mol %), Me-Phos, K_2CO_3 (2 equiv), 100 °C, PhMe/MeCN = 3:1]. However, a longer reaction time (24 h) was required to afford **1a** in reduced yield (50%). This control experiment clearly demonstrated the beneficial effect of microwave irradiation because the same compound **1a** can be isolated in quantitative yield after 1 h of microwave irradiation.

In summary, we have developed microwave-assisted intramolecular N-arylation conditions for the cyclization of 2-(*o*-iodophenyl)-2-acylamino acetamide. In combination with the versatile Ugi four-component reaction, highly functionalized 2-oxindoles with four diversity points can be easily prepared in two steps from readily accessible starting materials.

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Supporting Information Available: Experimental details, physical data, and copies of ^1H and ^{13}C NMR spectra of oxindoles. This material is available free of charge via the Internet at http://pubs.acs.org.

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