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Synthesis of 3-Aryl-8-oxo-5,6,7,8-tetrahydroindolizines via a Palladium-Catalyzed Arylation and Heteroarylation

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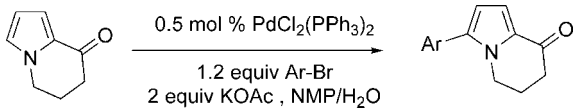


A selective palladium-catalyzed arylation and heteroarylation of 8-oxo-5,6,7,8-tetrahydroindolizines has been developed. Mechanistic studies assume an electrophilic substitution pathway for this transformation. This method provides an efficient one-step synthesis of 3-aryl-8-oxo-5,6,7,8-tetrahydroindolizines.

The 8-oxo-5,6,7,8-tetrahydroindolizine skeleton (Figure 1) was reported as a key intermediate in the synthesis of indolizidine building blocks[1] and natural indolizidine alkaloids such as the (+)-monomorine,[1g] indolizidine 209D,[1,2] or polygonatines A, B[1f] and kinganone.[1,3] Recently, 3-aryl-8-oxo-5,6,7,8-tetrahydroindolizines[4] were described as inhibitors of Hsp-90, an ATP-dependent chaperone responsible for the regulation of stabilization, activation, and degradation of a range of "client" proteins involved in cell cycle regulation and signal conduction.[5] Because many oncogenic proteins are substrates for Hsp-mediated protein folding processes, Hsp-90 has become an attractive target for novel cancer chemotherapeutics. Geldanamycin,[6] as well as aminoquinoline derivatives[7] and purine analogues,[8] have been identified as inhibitors of Hsp-90.

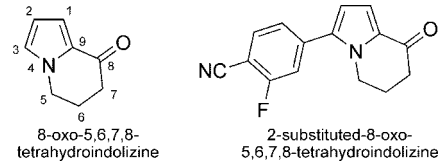
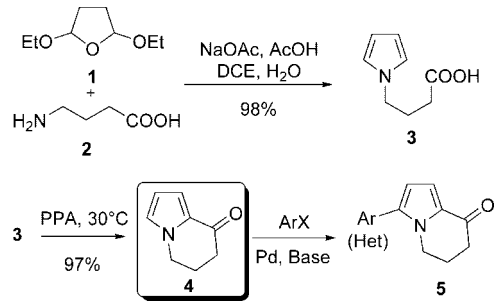


FIGURE 1. 8-Oxo-5,6,7,8-tetrahydroindolizine and Hsp-90 inhibitor.

To date, 3-aryl 8-oxo-5,6,7,8-tetrahydroindolizines has been obtained by a-four step strategy involving a Suzuki−Miyaura[9] coupling or a five-step procedure implementing a Müller−Polleux[10] preparation of pyrrole.

Herein, we disclose an alternative and pratical three-step strategy for the preparation of 3-aryl 8-oxo-5,6,7,8-tetrahydroindolizines **5** based on a direct arylation or heteroarylation of the tetrahydroindolizine intermediate **4** (Scheme 1). Among the different available methods for the formation of the tetrahydroindolizinone skeleton,[1−4] condensation of γ-amino butyric acid (GABA) with 2,3,4,5-tetrahydro-2,5-dimethoxytetrahydrofuran,[3] followed by the activation of the carboxylate group of the resulting γ-pyrrolic acid **3** with PPA (polyphosphoric acid) under modified Taylor conditions,[1c] was one of the most efficient routes, affording the key intermediate 6,7-dihydro-8(5*H*)-indolizinone **4** in an overall yield of 95%.

SCHEME 1. Preparation and Modification of 6,7-Dihydro-8(5*H*) indolizinone



Selective coupling of aryl and heteroaryl motifs at the C-3 position of the tetrahydroindolizine ring allowed access to the 3-aryl-8-oxo-5,6,7,8-tetrahydroindolizines. Although similar coupling reactions on various heterocyclic systems[10] such as furans,[11] thiophenes,[12] and indoles[13] have been described in the

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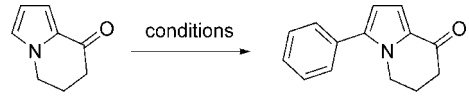
TABLE 1. Arylation of 4 with Bromobenzene



conditions	A	B	C	D
PhBr	1.8 equiv	1.2 equiv	1.2 equiv	1.2 equiv
catalyst	$Pd(OAc)_2$ 10%	$PdCl_2(PPh_3)_2$ 5%	$PdCl_2(PPh_3)_2$ 0.5%	$PdCl_2(PPh_3)_2$ 0.5%
KOAc	2.3 equiv	2 equiv	2 equiv	2 equiv
H_2O		2 equiv	0.2 equiv	0.2 equiv
additive	PPh_3 (0.02 equiv)			
solvent	DMF (0.9 M)	NMP (0.5 M)	DMF (1.8 M)	NMP (1.8 M)
reaction time	101 h	90 h	90 h	89 h
conversion	83%	70%	81%	>95%

literature, only few examples of the arylation of the pyrrole rings were reported, and most of them described the intramolecular aryl-pyrrolyl bond formation. However, some examples of intermolecular aryl-pyrrolyl bond formation were reported involving N-metalated pyrrole by Filippini[14] and N-free or N-methyl pyrrole by Ohta,[15] nevertheless with low yields. The first palladium-catalyzed selective arylation on 3-substituted indolizines was finally reported in 2004 by Park.[16]

As already performed in our laboratory on benzo[*b*]-thiophenes,[17] arylation of **4** with bromobenzene was initially examined using $Pd(OAc)_2$ (10 mol %) with various bases (K_2CO_3, Cs_2CO_3, Et_3N, Ag_2CO_3, NaOAc, CsOAc, KOAc) and additives including DCH18C6, NBu_4Br, or Ph_3P in DMF, MeCN, DMSO, DMA, or dioxane at different temperature varying from 80 to 130 °C. When the reaction was performed in DMF at 100 °C with KOAc (2.3 equiv) and Ph_3P (10 mol %) (Table 1, column A), an 83% conversion of the corresponding coupling adduct was observed.

Conditions reported by Park[16] on indolizines were also tested (column B), but the conversion was lower. Experiments were run with 0.5% of palladium complex and 0.2 equiv of water in DMF (column C) or in NMP (column D). Finally, the arylation of tetrahydroindolizinone proceeded more efficiently (>95% conversion and 88% isolated yield) in the presence of catalytic amounts of $PdCl_2(PPh_3)_2$ (0.5%), KOAc (2 equiv) and H_2O (0.2 equiv) in NMP (1.8 M) at 100 °C (column D).

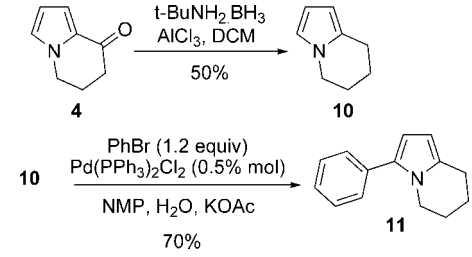
Based on a molecular modeling using semiempirical PM3 that showed that the highest charge density of the unsubstituted position of the pyrrole moiety was located at the 3-position (Figure 2), we assumed that the mechanism of the arylation is similar to that already proposed by Miura,[18] Li,[19] and Park.[16]

After oxidative addition of aryl bromide **6**, the mechanism involved an electrophilic attack by the resulting aryl-palladium bromide species **7** to the 3-position of the pyrrole ring to form the intermediate **8**. Deprotonation of **8** followed by a reductive elimination of aryl(tetrahydroindolizinone)palladium II **9** gave the expected 3-aryl 8-oxo-5,6,7,8-tetrahydroindolizines **5** and regenerated the palladium(0) catalyst.

Moreover, the pyrrole ring is predominantly arylated at the 3-position over the 2-position because attacking at the 3-position gives rise to a more stable arenium ion as assumed by Li.[19] Attacking at the 2-position would fail to give such a stable arenium ion.

As additional argument that could also support the involvement of electrophilic aromatic substitution, we attempted to perform the arylation of the corresponding deoxygenated tetrahydroindolizine obtained in 50% yield by the reductive deoxygenation of the 6,7-dihydro-8(5*H*)-indolizinone using *tert*-butylamine borane complex and $AlCl_3$[20] (Scheme 2).

SCHEME 2. Preparation of 2-Phenyl-5,6,7,8-tetrahydroindolizine



The charge density calculation using semiempirical PM3 modeling showed that the 3-position of **11** is more electronegative than that observed with **4** (Figure 2).

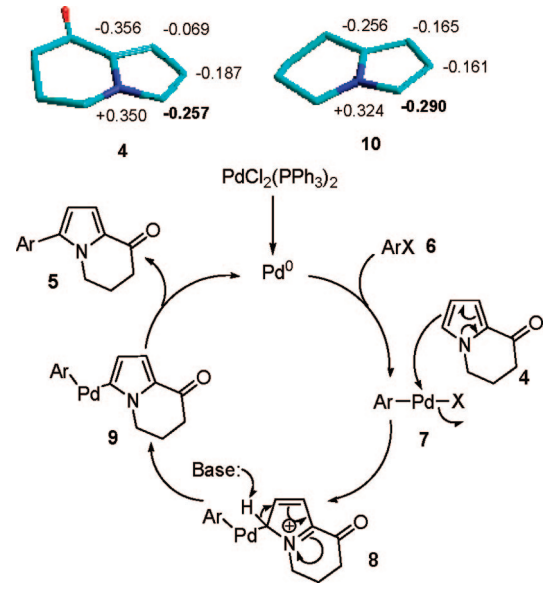


FIGURE 2. Calculated charge density.

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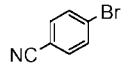
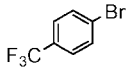
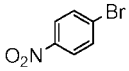
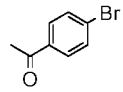
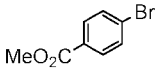
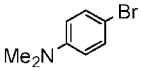
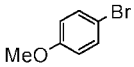
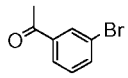
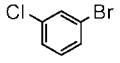
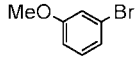
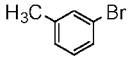
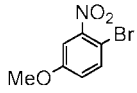
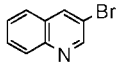
TABLE 2. Arylation of 6,7-Dihydro-8(5*H*)-indolizinone

Entry	Arylbromide	Reaction time	product	Conversion (%)[a]	Isolated yield (%)
1		89 h	**5a**	>95	88
2		31 h	**5b**	>95	93
3		31 h	**5c**	>95	79
4		90 h	**5d**	93	82
5		90 h	**5e**	85	71
6		31 h	**5f**	>95	84
7		120 h	**5g**	78	70
8		134 h	**5h**	17	-
9		134 h	**5i**	56	47
10		160 h	**5j**	<5	-
11		96 h	**5k**	90	84
12		51 h	**5l**	>95	94
13		80 h	**5m**	>95	91
14		160 h	**5n**	71	49
15		120 h	**5o**	20	-
16		89 h	**5p**	60	56
17		90 h	**5q**	81	[b]
18		48 h	**5r**	84	78
19		160 h	**5s**	<5	-
20		24 h	**5t**	>95	74

[a] Determined by ^{1}H NMR. [b] Degradation during purification was observed.

The arylation of **10** afforded the compound **11** in 95% conversion and 70% isolated yield in 18 h. This result could confirm that the mechanism of the arylation involved an electrophilic substitution.

The scope of the reaction was finally explored by applying the optimized reaction conditions to 6,7-dihydro-8(5*H*)-indolizinone **4** and various aryl bromides (Table 2). The effectiveness of the coupling reaction is strongly influenced by the electronic effects and the position of the aryl bromide substituents.

Electron-withdrawing groups at the *ortho* and *para* positions of the aryl bromide generally worked better (entries 2−7) than electron-donating groups in terms of the reaction times and yields (entries 8−10), in accordance with the Hammett coefficient.[21] Excellent conversion and isolated yields were also obtained with inductive electron-withdrawing groups at the *meta* position (entries 11−13), and a moderate conversion of 71% was reached with a methyl group (entry 14). Combining the effect of electron-withdrawing and electron-donating groups at the *para* and *ortho* positions gave **5p** in 56% yield (entry 16). On the other hand, poor conversion and isolated yield were obtained with a ketone substituent at the *ortho* position (entries 15), probably as a result of the steric hindrance resulting from the bulky group. Palladium-catalyzed heteroarylation of **4** with 3-bromopyridine and quinoline (entries 17 and 18) as well as the naphthalene coupling (entry 20) was more efficient than the thiophene coupling due to the electron-donating property of the sulfur atom. Consequently, electronic enrichment of the arylpalladium bromide species dramatically penalized the arylation conditions. This effect was less critical in the cases of the imidazopyrimidines[19] and indolizidines.[16] The reduced yields could be explained thanks to the charge density evaluation using semiempirical PM3. The electronegativity coefficient at the C-3 position of imidazopyrimidines of Li (−0.356) and C-2 position of indolizines of Park (−0.290) were higher than at the C-3 position of the tetrahydroindolizinone (−0.257). Therefore, electrophilic attacks were facilitated, and the enrichment of the arylpalladium halide species was less important. In conclusion, a new three-step highly divergent strategy was developed allowing the access to 3-aryl 8-oxo-5,6,7,8-tetrahydroindolizines, known for their inhibitive activity on the chaperone Hsp-90. From a palladium-catalyzed arylation and heteroarylation probably via an electrophilic aromatic substitution mechanism, indolizidines were obtained with global yields between 45% and 93%.

Experimental Section

Representative Procedure for Arylation of Compound 4. 8-Oxo-5,6,7,8-tetrahydroindolizine **4** (1 g, 7.35 mmol), KOAc (1.44 g, 14.7 mmol), $PdCl_2(PPh_3)_2$ (26 mg, 0.0367 mmol), and arylbromide (8.8 mmol) followed by freshly distilled NMP (4 mL) were added to a Schlenk flask under argon atmosphere. The mixture was stirred at 100 °C for 10 min. Then, water (23 μL, 1.3 mmol) was added to the solution. The reaction mixture was stirred at 100 °C for the appropriate time, diluted with dichloromethane (30 mL), and washed with water (3 × 10 mL). The organic layer was dried (Na_2SO_4), and the solvent was removed under reduced pressure. Purification by column chro-

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matography (silica gel, cyclohexane/ethyl acetate 8/2) afforded the desired compound **5a**−**t**. 3-Phenyl-8-oxo-5,6,7,8-tetrahydroindolizine (**5a**): 88%; white solid; mp = 121−122 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.17 (m, 2H), 2.55 (t, 2H, J = 6.2 Hz), 4.04 (t, 2H, J = 6.2 Hz), 6.27 (d, 1H, J = 4.1 Hz), 7.04 (d, 1H, J = 4.1 Hz), 7.37 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.9 (CH_2), 36.3 (CH_2), 44.5 (CH_2), 111.9 (CH), 114.7 (CH), 122.4 (CH), 125.9 (2 CH), 129.2 (2 CH), 132.4 (C_q), 135.4 (C_q), 137.5 (C_q), 187.9 (CO); IR 3056, 3029, 2946, 2880, 1646, 1532, 1508, 1454, 1384, 1333 cm^{-1}; HRMS[EI] calculated for $C_{14}H_{13}NO$ 211.0997, found 211.0998.

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Supporting Information Available: Experimental procedures, characterization data, and NMR spectra of all the new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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