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Convenient Synthesis of 3-Alkoxy-3-aryloxindoles by Intramolecular Arylation of Mandelic Amides

J. Mikael Hillgren and Stephen P. Marsden*

School of Chemistry, University of Leeds, Leeds LS2 9JT, United Kingdom

s.p.marsden@leeds.ac.uk

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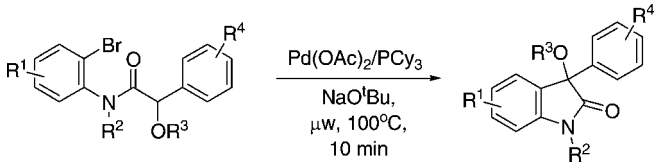
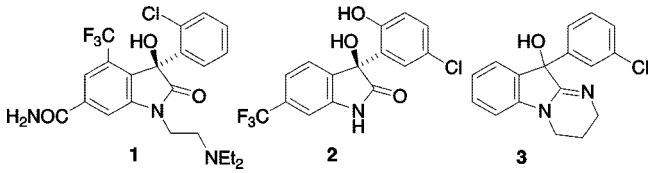


Medicinally important 3-alkoxy-3-aryloxindoles are conveniently prepared by the rapid microwave-promoted palladium-catalyzed intramolecular enolate arylation of mandelate-derived anilides.

3-Hydroxy- and 3-alkoxyoxindoles are found as core structures in a wide range of biologically active natural products[1] and pharmaceutical candidates. The 3-aryl-3-hydroxyoxindole skeleton in particular is found in several drug candidates, including the growth hormone secretagogue SM-130686 (**1**)[2] and the potassium channel opener **2**,[3] an early candidate in the program that led to the development of MaxiPost.[4] Hypoglycemic agents related to the antidepressant ciclazindol (**3**) can be accessed via 3-aryl-3-hydroxyoxindoles.[5]



The most commonly employed methods for the synthesis of this motif are the addition of aryl nucleophiles to isatins (Grignard reagents[6] and boronic acids[7]), inter-[8] and intramolecular[9] Friedel−Crafts hydroxyalkylations, oxidative hydroxylation of 3-aryloxindoles,[10] and S_NAr reactions of 2-fluoronitroarenes on dioxolanone templates.[11] Asymmetric variants of many of these approaches are known.[7a,b,10a,11]

The synthesis of 3,3-disubstituted oxindoles by palladium-catalyzed intramolecular arylation of anilide enolates developed by Hartwig[12] has received some attention from other workers.[13,14] Asymmetric variants of the reaction have been developed,[14] with recent developments using chiral *N*-heterocyclic carbene ligands giving usable (>90% ee) levels of enantioselectivity.[14d] To date, however, there has been only a single example of the arylation of an alkoxy-substituted enolate, specifically, the synthesis of a spirocyclic oxindole by arylation of a 2-carboxytetrahydrofuran derivative.[12b] Given our interest in the construction of quaternary centers by functionalization of oxygen-substituted enolates,[15] we wished to investigate the extension of enolate arylation chemistry to the synthesis of the valuable 3-alkoxy-3-aryloxindoles. Provided that the presence of the aryl substituent did not detrimentally affect the arylation process (for example by competing direct arylation), this would be an attractive convergent route to the target molecules, given the ready commercial availability of both substituted mandelic acid derivatives and *o*-haloanilines as building blocks. The potential for the development of asymmetric variants downstream was a further attraction. In this paper, we outline optimized conditions for the key transformation and report the scope and limitations of the process in terms of *O*- and *N*-substitution.

Initial screening studies on substrate **4a** identified that a 1:1 mixture of palladium(II) acetate and tricyclohexylphosphine (conveniently added as the air-stable phosphonium salt) was the most effective precatalyst combination. The reaction was further optimized in terms of base, solvent and temperature, and the results are summarized in Table 1.

In dioxane, the optimum base was found to be sodium *tert*-butoxide (entries 1−3). While the reaction could be carried out effectively under simple thermal heating (entry 4), we found that the reactions were more conveniently run under microwave irradiation, giving full conversion in only 10 min at a fixed

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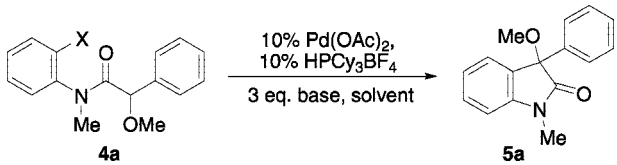
TABLE 1. Optimisation of Intramolecular Arylation of 4a

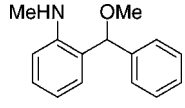


entry	X	solvent	base	*t* (°C)	time	conversion [a]	yield (%)
1	Br	dioxane	NaO^{t}Bu	70	22 h	100	70
2	Br	dioxane	LiHMDS	70	26 h	100	56
3	Br	dioxane	LiTMP	70	23 h	0	n/a
4	Br	dioxane	NaO^{t}Bu	85	1 h	100	73
5	Br	dioxane	NaO^{t}Bu	100[b]	10 min	100	77
6	Br	toluene	NaO^{t}Bu	100[b]	10 min	100	77
7	Br	toluene	LiHMDS	100[b]	10 min	100	58
8	Br	toluene	LiO^{t}Bu	100[b]	10 min	100	73
9	Br	THF	LiHMDS	100[b]	10 min	100	45
10	Br	TBME	LiHMDS	100[b]	10 min	100	53
11	Cl	toluene	NaO^{t}Bu	100[b]	10 min	10	n/a
12	I	toluene	NaO^{t}Bu	100[b]	10 min	100	91

[a] From crude ^{1}H NMR spectrum. [b] Carried out in microwave reactor (fixed temperature, variable power).

temperature of 100 °C (entry 5). Toluene was found to be a convenient solvent (entry 6) and was used thereafter since it is less harmful than dioxane. Sodium *tert*-butoxide was also found to be the best base in toluene (entries 6−8). Finally, we assessed the effect of changing the halide. While the aryl chloride gave very low conversion under the reaction conditions (entry 11), the corresponding iodide gave the best isolated yield at 91% (entry 12). However, since substituted 2-bromoanilines are both cheaper and more widely available than their iodo counterparts, we elected to conduct all future work on the bromoanilides.

In many of the above reactions, a small amount (ca. 5−10%) of a side product was isolated, which was identified as the diarylmethane **6**. This is presumed to arise by conversion of the oxindole product to the acyclic carboxylic acid, followed by decarboxylation. The carboxylic acid may be formed either by hydrolysis by adventitious water or ring opening by *tert*-butoxide followed by thermal cleavage of the *tert*-butyl ester.



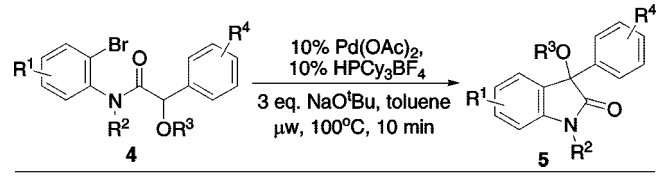
6

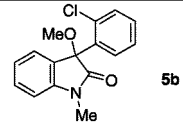
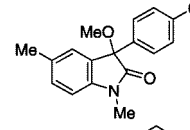
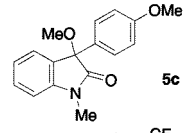
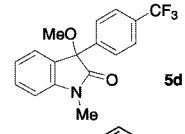
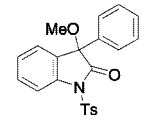
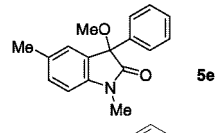
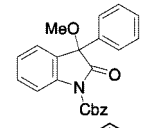
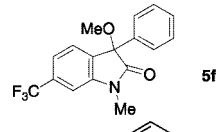
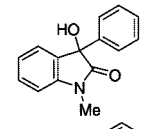
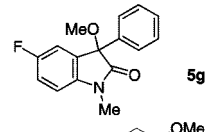
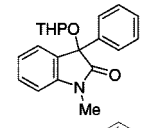
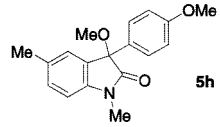
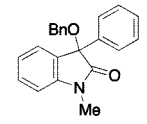
With a robust general procedure established, we next tested the substrate scope of the reaction. The requisite starting materials **4** were readily prepared by acylation of the (substituted) 2-bromoaniline with a hydroxyl-protected mandelic acid using triphenylphosphonium dichloride,[16] followed by protection (normally by N-methylation) of the resulting anilide.[12b] Fourteen further substrates were examined in the arylation using the optimized conditions and the results are summarized in Table 2.

The reaction tolerates a range of substituents (electron-withdrawing and -releasing) in the mandelate-derived aryl ring (entries 1−3). The presence of a chlorine substituent is not problematic (entry 1), which is significant both in terms of the presence of chloroarenes in the bioactive targets **1**−**3** and also as a potential handle for further functionalization of the products. Similarly, good yields of products were obtained with diverse substituents on the anilide ring (entries 4−6) or both aryl rings (entries 7 and 8).

Alternative nitrogen substituents were investigated (entries 9−11). While the *N*-benzyl substituent was well tolerated, the

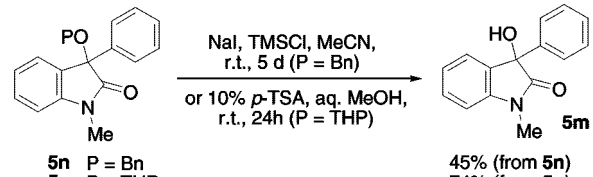
TABLE 2. Scope of Intramolecular Arylation Approach to 3-Alkoxy-3-aryloxindoles



entry	product	yield (%)	entry	product	yield (%)
1	 **5b**	76	8	 **5i**	75
2	 **5c**	71	9	 **5j**	86
3	 **5d**	56	10	 **5k**	0
4	 **5e**	86	11	 **5l**	0
5	 **5f**	81	12	 **5m**	0
6	 **5g**	79	13	 **5n**	73
7	 **5h**	71	14	 **5o**	73

presence of electron-withdrawing sulfonyl and Cbz substituents was not. Although no identifiable products were isolated from these reactions, we suspect that this is due to the enhanced pK_a (and hence leaving group ability) of the protected anilide leading to substrate cleavage, either by acyl substitution or α-elimination of the corresponding enolate.

Finally, since many of the bioactive targets have free C3-hydroxyl groups, the arylation was attempted on the unprotected substrate **4m**. The resulting reaction was extremely messy, however, and no identifiable products could be found. We therefore examined the performance of two potentially readily deprotected substrates **4n** and **4o** (entries 13 and 14). These returned good yields of oxindoles **5n** and **5o**, which could be deprotected under standard (and unoptimised) conditions to yield the desired free hydroxyoxindole **5m** (eq 1).



(1)

In summary, the intramolecular arylation of *o*-haloanilides has been extended to the novel synthesis of medicinally relevant 3-alkoxy-3-aryloxindoles. In particular, the results highlight the tolerance of the arylation protocol toward heteroatom substituents upon the enolate, of which there has only been a single prior example. The convergent nature of the synthesis (starting from readily available 2-bromoanilines and mandelic acid derivatives) coupled with the potential for asymmetric variants makes this an attractively convenient approach to this important class of molecules.

Experimental Section

General Procedure for Enolate Arylation. $Pd(OAc)_2$ (4.5 mg, 0.020 mmol) and $HPCy_3BF_4$ (7.4 mg, 0.020 mmol) were combined with sodium *tert*-butoxide (58 mg, 0.60 mmol) in a flame-dried 5-mL microwave tube. The tube was sealed with a septum and flushed with nitrogen, followed by the addition of degassed toluene (2 mL). The resulting solution was stirred at room temperature for 10 min, followed by the addition of the appropriate substrate **4** (0.20 mmol) dissolved in degassed toluene (2 mL). The mixture was subjected to microwave irradiation (fixed temperature of 100 °C, variable power) for 10 min. After cooling, the reaction mixture was filtered through a pad of Celite, washing with dichloromethane (50 mL), the filtrate was concentrated, and the residue was purified by silica gel chromatography.

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1,5-Dimethyl-3-methoxy-3-(4-trifluoromethylphenyl)-oxindole 5i. Yield 50 mg (75%), colorless solid, mp 97.6−97.8 °C (hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (2 H, d, J = 8.4 Hz), 7.48 (2 H, d, J = 8.4 Hz), 7.22 (1 H, dd, J = 7.9, 0.9 Hz), 7.03 (1 H, s), 6.84 (1 H, d, J = 7.9 Hz), 3.24 (3 H, s), 3.23 (3 H, s), 2.35 (3 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 142.9, 142.1, 133.3, 130.8, 130.4 (q, J = 32.2 Hz), 127.4, 126.7, 126.2, 125.3 (q, J = 3.7 Hz), 124.0 (q, J = 272.0 Hz), 108.5, 83.8, 53.1, 26.5, 21.1; IR (film) ν2935, 2829, 1728, 1500, 1326, 1124, 1103; HRMS *m*/*z* (EI+) found $[M + Na]^+$ 358.1016, $C_{18}H_{16}F_3NO_2Na$ requires 358.1025.

1-Benzyl-3-methoxy-3-phenyloxindole 5j. Yield 57 mg (86%), pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42−7.23 (12 H, m), 7.10 (1 H, td, J = 7.5, 0.9 Hz), 6.80 (1 H, dd, J = 8.4, 1.0 Hz), 4.93 (2 H, apparent d, J = 3.0 Hz), 3.28 (3 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 143.6, 138.8, 135.6, 130.0, 128.8, 128.43, 128.38, 128.1, 127.7, 127.3, 126.3, 125.8, 123.3, 109.6, 83.9, 53.2, 44.0; IR (film) ν 3054, 3027, 2930, 2824, 1725, 1611, 1466; HRMS *m*/*z* (EI+) found $[M + H]^+$ 330.1491, $C_{22}H_{20}NO_2$ requires 330.1489.

Acknowledgment. We thank the EPSRC (grant EP/D002818/1) for funding.

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

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