



Investigation of the N-arylation of various substituted indoles using microwave-assisted technology

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ABSTRACT

Various substituted indoles were reacted with activated aryl-fluorides using microwave-assisted technology in the construction of *N*-aryl bonds.

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According to the literature, there are several methods for the synthesis of *N*-aryl containing indoles,¹ such as transition metal-mediated couplings,^{2,3} nucleophilic aromatic substitutions,^{4,5} Ullmann type couplings,^{6,7} and indole ring formation of *N*-aryl containing compounds.⁸ Many of the cited methods suffered from low yields, problems with regioselectivity, purification difficulties or from a protracted number of steps in the synthesis. The nucleophilic aromatic substitution method mediated with potassium fluoride on alumina seemed a promising method because of the overall higher yields, toleration of a range of functional groups and the regioselectivity of the *N*-aryl bond formation over the C3-aryl bond formation.^{5,9} Smith et al. published a work focused on the effects of varied leaving groups and electron-withdrawing groups on the aryl-activated substrate.⁵ It was found that the leaving group ability of the fluoride was much better than that of other halogens for this reaction, which is in accordance with a nucleophilic aromatic substitution mechanism.¹⁰ With the assistance of microwave technology,¹¹ our lab focused on the effects of substitution on the indole ring itself for synthesizing *N*-aryl indole bonds using the method described by Smith.⁵

The reaction between 5-methoxyindole and either 4-fluorobenzamide or ethyl 4-fluorobenzoate was optimized using an Emrys Optimizer microwave (see 'typical procedure for the *N*-arylation of indoles' below) by varying reaction time, reaction temperature and equivalents of 18-crown-6. Increasing the reaction time from 1.5 h to 2.0 h improved the yields from 36% to 41% (examples 1 and 2, Table 1), and yields were subsequently improved by raising the reaction temperature from 160 °C to 180 °C as yields went from 41% to 64% (examples 2 and 3, Table 1).¹² Yields rose substantially going from 0.1 equiv of 18-crown-6 with a 26% yield to 2.0 equiv of 18-crown-6 with a 71% yield (examples 9–12, Table 1). It is important to use basic alumina for loading the potassium

fluoride in contrast to using commercially available 40% KF/Al₂O₃. When commercially available 40% KF/Al₂O₃ was used, yields in one example went from 71% to 37% (examples 4 and 12, Table 1), and in another example went from 79% to 10% (examples 15 and 16, Table 2).¹³ Yields were also improved (71% compared to 18%) when 14 equiv of KF was used in comparison to when 1 equiv of

Table 1
Optimization of 5-methoxyindole and activated aryl fluorides^a

Example	Time (h)	Temp (°C)	18-C-6 (equiv)	Solvent	EWG	Yield (%)
1	1.5	160	2.0	DMSO	-CO ₂ Et	36
2	2.0	160	2.0	DMSO	-CO ₂ Et	41
3	2.0	180	2.0	DMSO	-CO ₂ Et	64
4	2.0	180	2.0	DMSO	-CONH ₂	37 ^b
5	2.0	180	2.0	NMP	-CONH ₂	34
6	2.0	180	2.0	DMF	-CONH ₂	53
7	2.0	180	2.0	DMSO	-CONH ₂	18 ^c
8	2.0	180	2.0	DMSO	-CONH ₂	30 ^d
9	2.0	180	0.1	DMSO	-CONH ₂	25
10	2.0	180	0.5	DMSO	-CONH ₂	45
11	2.0	180	1.0	DMSO	-CONH ₂	57
12	2.0	180	2.0	DMSO	-CONH ₂	71

^a All yields are isolated yields, and unless otherwise noted, 2 equiv of aryl fluoride was used.

^b Commercially available 40% KF/Al₂O₃ was used.

^c 1 equiv of KF was used.

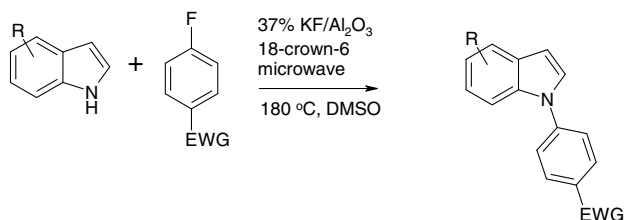
^d 1 equiv of 4-fluorobenzamide was used.

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Table 2

N-arylation of various substituted indoles and activated aryl fluorides



Example	EWG	R	Yield (%)	Example	EWG	R	Yield (%)
1	-CN	2-CO ₂ Et	10	2	-CONH ₂	2-Me	17
3	-CN	2-Me	48	4	-CONH ₂	4-CN	23
5	-CN	4-CN	33	6	-NO ₂	4-CN	44
7	-CONH ₂	4-CN	40	8	-CONH ₂	4-CN	23
9	-CO ₂ Et	4-Me	40	10	-CN	4-Me	71
11	-NO ₂	4-Me	78	12	-CONH ₂	4-Me	40
13	-CONH ₂	4-OMe	78	14	-CONH ₂	5-Br	30
15	-CONH ₂	5-CHO	79	16	-CONH ₂	5-CHO	10 ^a
17	-CO ₂ Me	5-Cl	24	18	-CO ₂ Me	5-CN	57
19	-CONH ₂	5-CN	0 ^b	20	-CONH ₂	5-CN	35 ^c
21	-CONH ₂	5-CO ₂ Et	47	22	-CO ₂ Me	5-CO ₂ Me	53
23	-CN	5-CO ₂ Me	24	24	-CO ₂ H	5-CO ₂ Me	0
25	-CONH ₂	5-H	45	26	-CO ₂ Me	5-H	49
27	-CN	5-OMe	68	28	-CONH ₂	5-OMe	71
29	-CO ₂ Me	5-OMe	64	30	-CO ₂ Et	5-OMe	37
31	-CO ₂ H	5-OMe	0	32	-NO ₂	5-OMe	0
33	-CONH ₂	6-CN	0	34	-CONH ₂	6-Me	72
35	-CN	6-NO ₂	35	36	-CONH ₂	6-OMe	45
37	-CO ₂ Me	7-Br	Trace	38	-CN	7-Br	50
39	-CONH ₂	7-Br	Trace	40	-CONH ₂	7-Me	12
41	-CONH ₂	7-OMe	15				

^a Commercially purchased 40% KF/Al₂O₃ was used.^b Cyano group on the product had hydrolyzed.^c Reaction temperature at 130 °C.

KF was used (examples 7 and 12, Table 1). Lastly, it was found that yields improved when 2 equiv of the aryl fluoride (example 12, Table 1) was used in comparison to when 1 equiv (example 8, Table 1) was used (71% vs 30% yield).

In coupling substituted indoles with activated aryl fluorides (Table 2), it was found that positions 4–6 gave similar yields to each other in comparative reactions. However, positions 2 and 7 gave much lower yields than the other investigated ones, which is most likely due to adverse steric interactions. It was also found that electron-donating groups on the indole generally gave higher yields than when electron-withdrawing groups were present. Given that the presumptive mechanism is S_NAr,^{5,14} it was expected that the more electron-rich indoles with electron-donating groups would generally have higher yields in comparison to the indoles with electron-withdrawing groups. Something to note is the variability of yields in ester containing substrates, as it is likely in some cases that the esters may have been hydrolyzed to a carboxylic acid. Also, it should be noted that cyano-substituted indoles were prone to hydrolyses. In one example, lowering the reaction temperature from 180 °C to 130 °C (examples 19 and 20, Table 2) reduced the extent of hydrolyses, where the yields went from 0% to 35%.

In summary, we have explored the scope and reactivity of variously substituted indoles using an N-arylation methodology mediated with potassium fluoride on basic alumina using microwave-assisted technology. The reactivity of the substituted indoles

is 4 ≈ 5 ≈ 6 ≫ 2 ≈ 7, and the yields of indoles with electron-donating groups were generally higher than those of on indoles with electron-withdrawing groups. Lastly, in groups prone to hydrolyses, it is advisable to reduce the reaction temperature to minimize this side reaction.

Typical procedure for the N-arylation of indoles: To a 20 mL vial equipped with a teflon-coated stir bar were added 5-methoxyindole (1 mmol), 4-fluorobenzamide (2 mmol), 18-crown-6 (2 mmol), 37% KF/Al₂O₃ (2.0 g) (see note 13 for a method for preparation of 37% KF/Al₂O₃), and DMSO (15 mL). The vial was flushed with nitrogen, sealed with a cap, placed in the microwave and heated at 180 °C for 2 h¹² (An Emrys Optimizer was used in these reactions,¹⁵ and the power varied between 0 and 300 W while the pressure for these reactions did not exceed 5 atm). The vial was uncapped, and the mixture was diluted with ethyl acetate (20 mL) and filtered. The filtrate was washed with water (20 mL) and brine (20 mL), and then dried with MgSO₄. After filtration and concentration, the crude mixture was purified by preparative HPLC.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2008.10.053](https://doi.org/10.1016/j.tetlet.2008.10.053).

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