Heterocycles

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Catalyst-Free N-Arylation Using Unactivated Fluorobenzenes**

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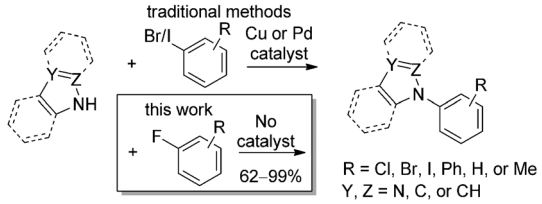
N-arylation of heteroaromatic compounds is an extremely important C–N bond-forming reaction in organic synthesis, especially with N-arylated azole and indole derivatives finding important uses (Scheme 1) as inhibitors of enzymes[1] (e.g. COX-1,[1a] COX-2,[1b] PDE3,[1c] PDE5,[1d] topoisomerase II[1e]), inhibitors of ATP binding,[2] agonists or antagonists of G protein-coupled and other receptors[3] (e.g. DA D-2,[3a] 5-HT_2,[3b] α_1AR,[3a] CB_1,[3b,c] Sigma σ2,[3d] $GABA_A$[3e]), modulators of ion-channels,[4] as key components in LED production,[5] and for creating organometallic catalysts.[6] N-arylated azole and indole derivatives are also registered pharmaceuticals (e.g. celecoxib, midazolam, flumazenil, nilotinib, edaravone, alprazolam, sertindole; Figure 1) and insecticides or fungicides (e.g. pyraclofos, pyraclostrobin).

N-arylated azole and indole derivatives are most commonly synthesized from iodobenzene or bromobenzene derivatives by transition-metal-catalyzed cross-coupling reactions such as copper-catalyzed Ullmann-type N-arylation or palladium-catalyzed Buchwald–Hartwig coupling.[7] However, transition-metal-catalyzed N-arylation has some drawbacks in industrial applications as it is expensive, oxygen sensitive, and may leave toxic trace metal contaminants. In addition, the synthesis of bromo- or iodo-substituted N-arylated azole derivatives is difficult using metal-catalyzed cross-coupling, which relies upon selective monosubstitution of benzene rings having two or more iodo/bromo substituents.[8]



Scheme 1. Catalyst-free N-arylation using monofluorobenzenes.

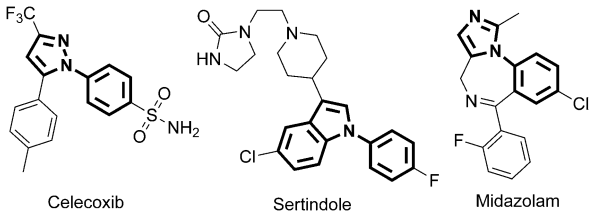


Figure 1. Examples of N-arylated registered pharmaceuticals.

Catalyst-free N-arylation has been effected by S_NAr substitution on highly electron-deficient fluorobenzene derivatives having additional electron-withdrawing groups, such as nitro, carbonyl, sulfonyl, nitrile, or fluoro,[9] but reported methods give low yields for less activated fluorobenzene derivatives and are not feasible for unactivated fluorobenzenes.[10] However, we find that under optimized reaction conditions, in which the choices of base and solvent play key roles, these reactions occur rapidly and with full conversion. Herein we describe a simple, high yielding, catalyst-free N-arylation reaction in which fluorine is displaced from unactivated fluorobenzenes by azole and indole derivatives (Scheme 1). This reaction also tolerates a wide range of substituents on the azole or the fluorobenzene (including bromo and iodo), thus making it a highly versatile and high yielding synthetic method for N-arylation.

N-arylation was initially optimized herein using 4-bromofluorobenzene, which has been reported in numerous copper- or palladium-catalyzed N-aryl cross-coupling reactions involving the displacement of bromine.[11] Here, we instead selectively displace fluorine with azole or indole derivatives in dipolar aprotic solvents containing a simple inorganic base (Tables 1 and 2). The reaction proved to be very robust, thus tolerating a diverse range of inorganic bases, polar aprotic solvents, and reaction temperatures. However, it was found that the *N*-(4-bromophenyl)-benzimidazole product (**1**) was prone to undergoing additional transformations. To prevent ongoing reactions, conditions had to be optimized to achieve full conversion, short reaction times, and high yields. Monitoring crude reaction mixtures by HPLC and LCMS enabled rapid identification of reaction progress and product formation (see Supporting Information). As a base, potassium phosphate was superior to a range of other potassium bases, with carbonate giving poor conversion, and hydroxide and especially *tert*-butoxide giving good conversion but with substantial amounts of by-products (Table 1 and Supporting Information). The corresponding sodium salts had similar reactivity, and lithium salts followed the same trends but with lower conversion (see Supporting Information). Cesium carbonate was superior to other carbonate salts, and reactions were a little faster than that using potassium phosphate. DMF or DMA were most effective and efficient for product

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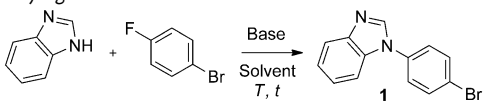
Table 1: Varying reaction conditions.[a]

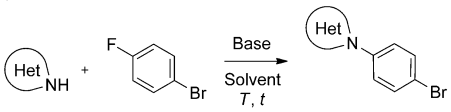


1

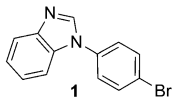
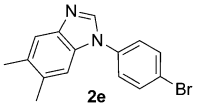
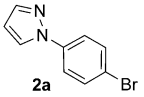
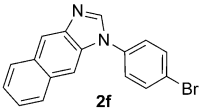
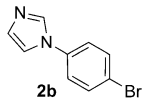
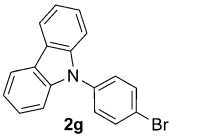
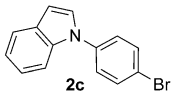
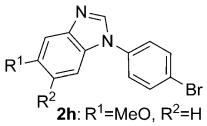
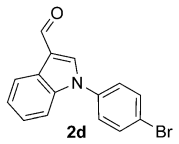
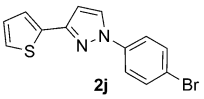
Entry	Base	Solvent	T [°C]	t [h]	Conv. [%][b]	Yield [%][c]
1	K_3PO_4	DMF	190	0.5	88	88
2	KOH	–	–	–	61	38
3	KO*t*Bu	–	–	–	81	29
4	KF	–	–	–	< 5	–[d]
5	Li_2CO_3	–	–	–	< 5	–[d]
6	Na_2CO_3	–	–	–	15	–[d]
7	K_2CO_3	–	–	–	11	–[d]
8	Cs_2CO_3	–	–	–	97	88
9	K_3PO_4	DMF	170	1	75	75
10	–	DMA	–	–	87	83
11	–	NMP	–	–	27	17
12	–	DMSO	–	–	64	53
13	–	1,4-dioxane	–	–	< 1	–[d]
14	K_3PO_4	DMF	140[e]	24	90	90
15			150[e]	16	> 99	93
16		–	170	4	99	95
17	–	–	190	1	99	91
18		–	210	0.25	96	90
19	Cs_2CO_3	DMA	170	1	> 99	88

[a] Reaction conditions: benzimidazole (0.5 mmol), 4-bromo-fluorobenzene (2 equiv), base (5 equiv), solvent (5 mL), microwave heating. [b] Conversion of benzimidazole determined by HPLC (see Supporting Information). [c] Yield of **1** determined by HPLC (see Supporting Information). [d] Not assessed because of low coversion. [e] Conventional heating instead of microwave. DMA = *N*,*N*′-dimethylacetamide, DMF = *N*,*N*′-dimethylformamide, DMSO = dimethylsulfoxide, NMP = *N*-methylpyrrolidone.

Table 2: N-arylation of azoles or indoles with 4-fluorobromobenzene.[a]



1, 2a-g

Product	Cond.	Yield [%][b]	Product	Cond.	Yield [%][b]
 **1**	A B	89 93	 **2e**	A	84
 **2a**	A B	71 72	 **2f**	A	79
 **2b**	A B	91 88	 **2g**	C	91
 **2c**	A B	87 81	 **2h**: R^1=MeO, R^2=H **2i**: R^1=H, R^2=MeO	A	94
 **2d**	A	78	 **2j**	A	89

[a] Reaction conditions: azole (0.5 mmol), 4-bromo-fluorobenzene (2 equiv), and either A) K_3PO_4 (5 equiv), DMF (5 mL), 190 °C, 1 h, microwave, or B) K_3PO_4 (5 equiv), DMF (5 mL), 150 °C, 16 h, conventional heating, or C) Cs_2CO_3 (5 equiv), DMA (5 mL), 190 °C, 16 h, microwave; [b] Yield of isolated product.

formation with minimal amounts of by-products, but DMSO promoted by-product formation and NMP gave much slower conversion. The reaction proceeded at 140–210 °C, however by-product formation increased slightly at the higher temperatures. The reaction was insensitive to one equivalent of water, but was prevented in a 1:4 mixture of H_2O/DMF as the solvent mixture.

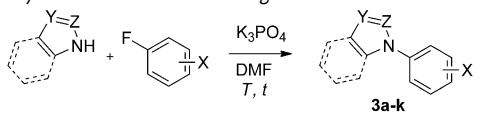
Lowering the energy barrier to formation of the intermediate Meisenheimer sigma complex is known to be important in facilitating S_NAr reactions.[9a] It was found that reaction rates were enhanced by adding excess potassium phosphate, even changing from 2 to 5 equivalents had a pronounced effect. It was also noted that the reaction rate was slower with potassium *tert*-butoxide, which is quite soluble and fully deprotonates benzimidazole under the reaction conditions, than with potassium phosphate or cesium carbonate. Thus, base not only deprotonates the azole/indole derivative but also has additional effects on the reaction rates.

Detailed LCMS and HPLC studies (see Supporting Information) proved that nucleophilic attack proceeds preferentially on the fluorine-substituted carbon atom of the bromobenzene ring, thus leading to the desired product **1** with no trace of *N*-(4-fluorophenyl)-benzimidazole observed. However, small amounts of phenol derivatives and *N*,*N*-dimethyl-bromo-aniline were also generated, presumably through attack on 4-bromofluorobenzene by small amounts of competing nucleophiles. Depending upon reaction conditions, varying amounts of disubstituted and debrominated products were also observed. It is proposed that substitution of bromine occurs through benzyne formation, which then is attacked by a second nucleophile (S_NEA mechanism) to form disubstituted dehalogenated benzene derivatives. This is supported by recent reports using other bromo- and iodobenzene derivatives.[12] Nevertheless, the optimized reaction conditions identified herein gave high yields of the desired *N*-(4-bromophenyl)-benzimidazole (**1**; Table 1, Table 2).

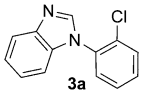
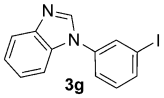
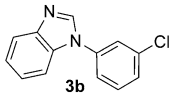
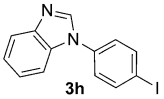
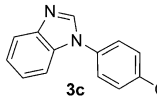
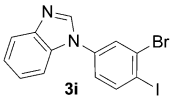
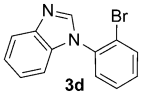
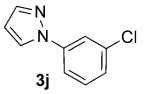
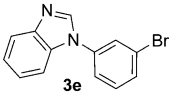
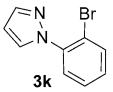
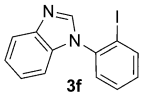
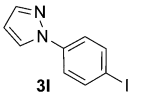
The optimized reaction conditions were also applied in the N-arylation of a range of substituted azole and indole derivatives, thus successfully converting them into one major product in good to excellent yields (Table 2). In general, N-arylation was not affected by the nature of the substituents on either azoles or indoles, thus giving products with electron-withdrawing or electron-donating substituents (Table 2).

To extend the scope of N-arylation, 4-fluorobromobenzene was replaced with a series of other halogenated fluorobenzenes. Gratifyingly, each reacted under the optimized reaction conditions to give the corresponding N-phenyl benzimidazole or pyrazole derivative in good to excellent

Table 3: N-arylation of azoles with halogenated fluorobenzenes.[a]

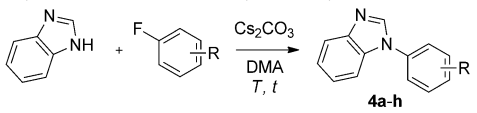


3a-k

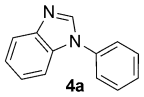
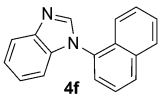
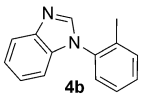
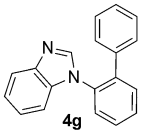
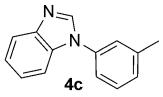
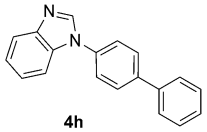
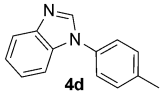
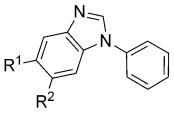
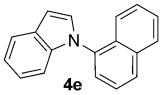
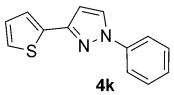
Product	Cond.	Yield [%]	Product	Cond.	Yield [%]
 **3a**	A B	98[b] >95[c]	 **3g**	A B	62[b] 73[c]
 **3b**	A B	93[b] >95[c]	 **3h**	A B	84[b] 91[c]
 **3c**	C B	94[b] 82[c]	 **3i**	D	80[b]
 **3d**	A B	86[b] 90[c]	 **3j**	A	>99[b]
 **3e**	A	79[b]	 **3k**	A	83[b]
 **3f**	A	91[b]	 **3l**	A	72[b]

[a] Reaction conditions: azole (0.5 mmol), fluorobenzene derivative (2 equiv), K_3PO_4 (5 equiv), DMF (5 mL) and either A) 190 °C, 1 h, microwave, or B) 150 °C, 24 h, heating block, or C) 190 °C, 2 h, microwave, or D) 170 °C, 1 h, microwave. [b] Yield of isolated product. [c] Determined by HPLC.

Table 4: N-arylation of azoles with alkyl- and aryl-fluorobenzenes.[a]



4a-h

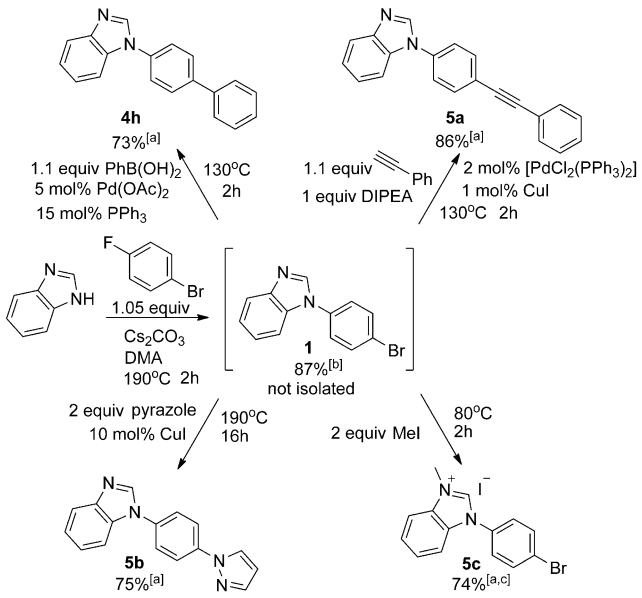
Product	Cond.	Yield [%][b]	Product	Cond.	Yield [%][b]
 **4a**	A	>99	 **4f**	E	99
 **4b**	B	92	 **4g**	E	95
 **4c**	B	>99	 **4h**	E	98
 **4d**	C	>99	 **4i**: R^1=MeO, R^2=H **4j**: R^1=H, R^2=MeO	F	81
 **4e**	D	98	 **4k**	A	96

[a] Reaction conditions: azole (0.5 mmol), fluorobenzene derivative, Cs_2CO_3 (2.5 mmol), DMA (5 mL), microwave and either A) 2.5 mmol, 190 °C, 16 h, or B) 2.5 mmol, 210 °C, 12 h, or C) 5 mmol, 210 °C, 24 h, or D) 1 mmol, 210 °C, 12 h, or E) 1.0 mmol, 190 °C, 16 h, or F) 1.0 mmol, 190 °C, 12 h. [b] Yield of isolated product.

yields (Table 3). These findings are important because bromo- and iodo-substituted N-phenyl azole derivatives are difficult to synthesize by other methods. In general, replacement of fluorine did not affect the the other halogen substituent, there was no loss of chlorine, and only *meta*-substituted bromo and iodo products showed significant loss of halogen. However, these *meta*-substituted products were still obtained in good yields under optimized reaction conditions. Interestingly, the reaction with 2-bromo-4-fluoro-iodobenzene showed little loss of halogen and gave full conversion at 170 °C after 1 hour. N-phenyl azole products with a bromo and an iodo substituent are very difficult to obtain through other methods with **3i** being, to our knowledge, the first example of this kind.

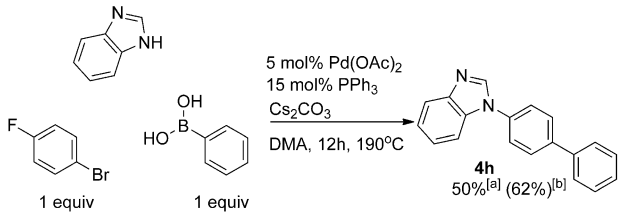
Encouraged by the success with halogenated fluorobenzene derivatives, substituents other than a halogen were also examined for effects on reactivity. A series of unactivated fluorobenzenes were tested and no further transformation of the product was observed despite the extended reaction times (Table 4). Interestingly, even fluorobenzene reacted under the conditions with full conversion and excellent product yields (Table 4). To our knowledge, this is the first example of a quantitative, catalyst-free, synthesis of N-phenyl derivatives of any type of azole. Even the fluorotolyl derivatives, with an electron-donating methyl group, underwent full conversion within 24 hours albeit at higher temperatures. Fluorine-substituted biphenyl and naphthyl derivatives also gave full conversion to the desired products in excellent yields upon isolation. Methoxy and thiophenyl substituents were untouched even under prolonged reaction times (**4i**/**4j** and **4k**). The electronic effect of the methoxy substituent had little impact on regioselectivity, thus resulting in approximately 1:1 mixture of **4i**/**4j**. In contrast, a bulky 3-thiophenyl group on pyrazole leads to one product (**4k**; Table 4). Compounds **3b**, **4a**, **4b**, and **4i** are known inhibitors of ATP binding to the platelet-derived growth factor receptors (PDGFRs),[2] which are targets in cancer, vascular disorders, and fibrotic diseases.[13] Previously **4i** was synthesized in three steps by a cross-coupling reaction.[2] We envisage that the present methodology may be useful for developing new PDGFR inhibitors.

Because of the high purity of the crude *N*-(4-bromophenyl)-benzimidazole products, we envisaged that additional transformation by cross-coupling reactions could be effected in the same pot without the need for an intervening purification step. This was indeed the case, exemplified here for Suzuki coupling, Sonogashira coupling, Ullmann-type reactions, and a simple N-alkylation (Scheme 2). All these reactions proceeded successfully to the desired products in good yields and with no significant by-products. To explore



Scheme 2. Scope of one-pot reactions. [a] Yield of isolated product (after 2 steps). [b] Determined by HPLC. [c] Trifluoroacetate salt after purification.

the orthogonality of this reaction further, N-arylation by S_NAr substitution and transition-metal-catalyzed cross-coupling reactions were conducted simultaneously in one pot (Scheme 3). This gave the desired product in reasonable yield, thus proving that N-arylation by S_NAr substitution and C–C bond formation through transition-metal-assisted cross-coupling conditions can be done simultaneously. This capacity to perform C–N and C–C bond-forming reactions together in one pot, either simultaneously or in tandem, potentially makes this newly developed method even more versatile and extremely valuable for opening up multiple organic transformations to faster and cheaper one-pot approaches.



Scheme 3. Simultaneous S_NAr substitution and cross-coupling. [a] Yield of isolated product. [b] Yield corrected for unconverted benzimidazole.

In conclusion, a valuable and very simple new catalyst-free method for N-arylation of azole and indole derivatives has been described using direct S_NAr substitution of fluorine on unactivated benzene derivatives. Reaction conditions have been optimized to effect facile, rapid, versatile, and high-yielding, one-step reactions which tolerate a wide range of substituents on the fluorobenzene and azole/indole derivative, including chloro, bromo, and iodo substituents which result in halogenated N-aryl derivatives. This catalyst-free N-arylation reaction is also compatible with metal-catalyzed cross-coupling reactions performed in the same pot simultaneously with, or subsequent to, S_NAr substitution of fluorine in fluorobenzene derivatives. We predict that these new methods may have wide synthetic utility across organic, medicinal, agricultural, and polymer chemistry as well as in materials science applications.

Experimental Section

General procedure for S_NAr N-arylation using monofluorosubstituted benzene: Base was added to a glass vial containing the azole/indole derivative and the fluorobenzene derivative in dry solvent (5 mL). The vial was sealed with a teflon cap and the mixture was heated by microwave (0–250 W) or conventional heating while stirring. The mixture was cooled to RT, treated with 10 mL H_2O, and extracted with diethyl ether (4 × 5 mL). The solvent was removed and the crude reaction mixture was purified by vacuum liquid chromatography on silica gel using a 0–100% gradient of petrol ether and EtOAc.

Other experimental procedures, HPLC chromatograms, and ^1H and ^{13}C NMR spectra and data are provided in the Supporting Information.

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