

Efficient Nucleophilic Aromatic Substitution between Aryl Nitrofluorides and Alkynes

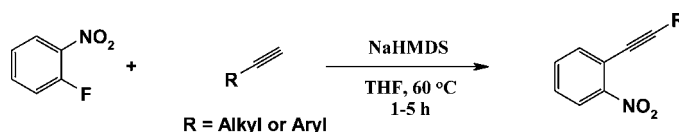
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ABSTRACT



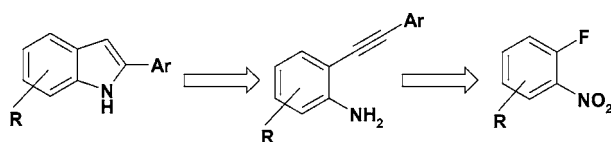
The nucleophilic aromatic substitution reaction between electron-deficient aryl fluorides and terminal alkynes is shown to be efficiently promoted by sodium bis(trimethylsilyl)amide as a base. Moderate to excellent yields of 2-ethynynitrobenzene products can be obtained under mild conditions.

Interest in indole-containing structures arises from their widespread abundance in natural products and as useful pharmacophores in medicinal chemistry.¹ The synthesis of the indole core has attracted much attention from the modern synthetic chemistry community and from medicinal chemists in particular, leading to the development of new methodologies.² We were particularly interested in the design of indole-based libraries using readily available starting materials. The indole core can be obtained via intramolecular cyclization of *o*-amino alkynyl derivatives, using a diverse set of catalysts such as indium,³ palladium,⁴ or gold⁵ as shown in Scheme 1. The required *o*-amino alkynyl intermediates can

nucleophilic aromatic substitution of readily available *o*-fluoronitrobenzenes could lead to the key nitro alkynyl derivatives. These intermediates are easily transformed to the desired indole precursor.

To date few examples of Sonogashira-type coupling have been reported in the absence of transition metal catalysis. Indeed, Leadbeater and co-workers⁷ published the first examples using microwave irradiation and sodium hydroxide in aqueous poly(ethylene glycol). Prajapati et al.⁸ have shown that indium trichloride could be efficiently used to catalyze the Sonogashira coupling in the absence of copper salt,

Scheme 1



be obtained via the Sonogashira reaction⁶ of the corresponding *o*-haloanilines. Driven by the need for a general and facile alternative to the Sonogashira method we envisaged that the

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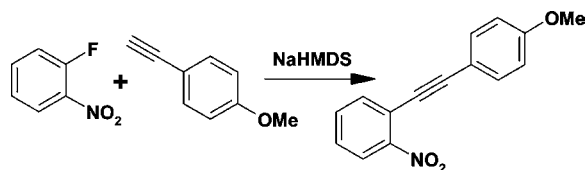
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Table 1. Optimization Study^c

entry	solvent	<i>T</i> (°C)	time (h)	yield (%) ^a
1	THF	rt	23	78
2	toluene	rt	23	52
3	THF	65	2	79
4	THF ^b	rt	23	75

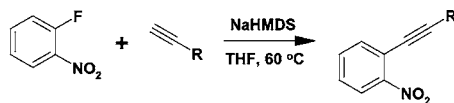
^a Isolated yields (average of 2 runs). ^b NaHMDS was first added to a solution of the alkyne. After 5 min, 2-fluoronitrobenzene was then added.

^c Reaction conditions: NaHMDS (1.5 equiv) was added to a mixture of the starting materials.

phosphine, and palladium. Wang and Pinhua⁹ have also reported a novel reaction utilizing silver iodide in the presence of triphenylphosphine and potassium carbonate to afford the coupling products in high yields. More recently tetrabutylammonium fluoride¹⁰ was used as a catalyst to

activate trimethylsilyl phenylacetylene toward nucleophilic substitution but provided only very low yield of the desired adduct. We decided to investigate the use of the alkynyl group in the S_NAr¹¹ reaction under anionic conditions. To our surprise, this transformation although simple had little precedent in the literature. However, given that lithium acetylides have previously been incorporated onto arene–Cr(CO)₃ complexes by S_NAr displacement¹² and the analogy between nitroarenes and arene–Cr(CO)₃, it prompted us to investigate this process. In this report, we describe the scope and limitation of this reaction.

We began our study by investigating the base and solvent required for this reaction. To our delight an initial attempt in which sodium bis(trimethylsilyl)amide (NaHMDS)¹³ was added to a mixture of 2-fluoronitrobenzene and 4-ethynylanisole in THF (Table 1, entry 1) provided a good yield of the desired coupling product. A screen of different solvents indicated that THF and toluene were the best choices, although toluene generally provided a lower yield of adduct at room temperature (Table 1). The reaction in THF was accelerated 10-fold by increasing the temperature to refluxing conditions, (entry 3, Table 1). The sequence of addition of the base did not impact the reaction outcome. Indeed, the

Table 2. S_NAr of 2-Fluoronitrobenzene with Functionalized Alkynes^d

Entry	Alkyne	Time (h)	Yield (%) ^a	Entry	Alkyne	Time (h)	Yield (%) ^a
1		1	80	9 ^b		1	83
2		1	78	10		1.5	77
3		2	85	11 ^b		1	60
4		1.5	74	12		2	40
5		1	53	13		1	56
6		2	67	14 ^b		2	78
7		2	58	15 ^b		2	83
8		1	59	16 ^{b,c}		5	95

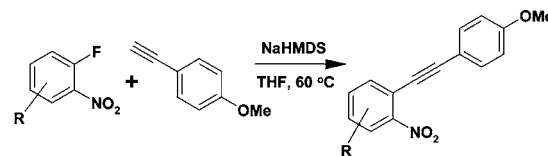
^a Isolated yields (average of 2 runs). ^b 2.0 equiv of NaHMDS was used. ^c Reaction time was 5 h. ^d Reaction condition: NaHMDS (1.5 equiv) was added to a mixture of the starting materials.

formation of the alkynyl anion prior to addition of 2-fluoro-nitrobenzene afforded the desired compound in a comparable yield (entry 4 vs entry 1). Replacement of the 2-fluoro-nitrobenzene by the analogous chloro, bromo, or iodo compound unfortunately did not provide the desired coupling product under different reaction conditions.¹⁴ The observed chemoselectivity limits the scope of this methodology but provides complementarity with the Sonogashira reaction.

Encouraged by the ease of this reaction, we next focused on expanding the scope of the methodology. Table 2 highlights the broad range of the various alkynes that can be used in the S_NAr reaction. Phenylacetylene provided the desired adduct in excellent yield (Table 2, entry 1). The addition of electron-withdrawing or electron-donating groups on the phenylalkyne did not alter the course of the reaction (entries 2–6). A notable exception was observed with the presence of a cyano group (entry 5); only a modest 53% yield of the coupled product was obtained, along with a number of undefined byproducts. In addition, the presence of an *ortho* substituent gave slightly lower yields (entries 7 and 8). On the other hand, the presence of a bromine atom at the *meta* position (entry 9) did not interfere with the reaction conditions, and provided an extra handle for further elaboration, using for instance palladium-catalyzed processes. It is of particular interest that a coupling under Sonogashira reaction conditions between 2-fluoronitrobenzene and 4-bromo-1-fluoro-2-nitrobenzene gave a 12 to 1 mixture in favor of the bromo displacement product. This result further substantiates the complementarity of these methodologies. It was also gratifying to observe the tolerance of this reaction to aromatic heterocycles. Indeed, the use of 3-ethynylpyridine and 2-ethynylthiophene gave the desired adducts in 77% and 60% yield, respectively (entries 10 and 11). The reaction could also be performed with nonaromatic alkynyl derivatives in moderate to almost quantitative yields (entries 13–16).

Finally, we probed the S_NAr reaction of 4-ethynylanisole with sterically hindered 2-fluoronitrobenzene derivatives. As illustrated in Table 3, the presence of a substituent *ortho* to the fluorine atom did not negatively impact the reaction and afforded excellent yields of the alkynyl derivatives (entries 1 and 2). It is worth noting that the presence of a trifluoromethyl group or a bromine atom *para* to the fluorine did not greatly influence reactivity (entries 3 and 4). In addition, chemoselective reaction was observed with 2-chloro-6-fluoronitrobenzene; substitution took place exclusively at the most electrophilic carbon and generated the desired adduct (entry 5).

Table 3. S_NAr of Functionalized 2-Fluoronitrobenzenes with 4-Ethynylanisole^b



Entry	Aryl fluoride	Product	Yield (%) ^a
1			75
2			79
3			71
4			60
5			71

^a Isolated yields (average of 2 runs). ^b Reaction conditions: NaHMDS (1.5 equiv) was added to a mixture of the starting materials.

In summary, we have successfully demonstrated that the nucleophilic aromatic substitution reaction between electron-deficient 2-fluoronitrobenzene derivatives and terminal alkynes can be efficiently performed via deprotonation using sodium bis(trimethylsilyl)amide as a base. This novel C–C bond formation reaction provides moderate to excellent yields of the corresponding 2-ethynylnitrobenzene adducts under facile conditions and short reaction times. The versatility of this reaction allowed us to efficiently prepare indole-containing compounds which are subsequently evaluated as novel xenobiotics. Results from these studies will be reported in due course.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(14) The 2-chloro derivative gave only recuperated starting material, and decomposition was observed with 2-iodo and 2-bromo derivatives.