

N-Arylation of Amines with *o*-Silylaryl Triflate

Y.G. LEE¹, D.I. JUNG^{1,*} and J.T. HAHN²

¹Department of Chemistry, Dong-A University, Busan 604714, Republic of Korea

²Department of Beautycare, Youngdong University, Youngdong 370701, Republic of Korea

*Corresponding author: Tel./Fax: +82 51 2007249; E-mail: dijung@dau.ac.kr

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An efficient, transition-metal-free procedure for the N-arylation of amines **1** has been achieved by allowing those substrates to react with *o*-silylaryl triflate **2** in the presence of CsF. Good to excellent yields of arylated products **3** are obtained under very mild reaction conditions. This chemistry readily tolerates a variety of functional groups.

Key Words: N-Arylation, *o*-Silylaryl triflate, CsF, Amines.

INTRODUCTION

Establishing an efficient, reliable method for the N-arylation of amines is currently active area of research in organic synthesis. Such aryl subunits are commonly found in a variety of biologically active and natural compounds¹, agrochemicals², HIV-1 protease inhibitors and compounds³ of interest in material science.

Traditionally⁴, the N-arylation of amines has been carried out under copper-mediated Ullmann-type conditions involving the coupling of amines with aryl halides⁵. Although these copper promoted reactions are useful, they usually require harsh reaction conditions and stoichiometric amounts of copper and the yields are not very reproducible⁶. Recently, a number of valuable new methods have been developed for the N-arylation of amines⁷. Buchwald and Hartwig^{8,9} have demonstrated that the Cu- or Pd-catalyzed N-arylation of a variety of amines by aryl halides is a powerful method for the synthesis of arylamines. Despite these significant recent improvements, there still are limitations in present N-arylation methods. For example, it is still difficult to present N-arylation methodology may not accommodate certain organic functionality. Of the functional groups that are incompatible with the Cu- or Pd catalyzed N-arylation methodology, the most important are probably halides. Most reaction conditions are fairly harsh, usually requiring high temperatures (> 110 °C) and strong polar and often toxic solvents. The direct coupling of aromatic carboxylic acids and aryl halides or the carbonylation of aryl halides with a palladium catalyst to generate the corresponding aryl esters is difficult¹⁰. In the classical methods for esterification, a strong acid, such as sulfuric acid, is needed, which is

not suitable for acid-sensitive compounds, can be corrosive and often produces side reactions, such as carbonization¹¹. In this paper, we report an efficient and reliable procedure to N-arylate amines under mild reaction conditions. Recently, silylaryl triflate **2**¹² has been employed to generate benzyne under mild reaction conditions, which can easily undergo a variety of synthetically useful nucleophilic¹³ and cycloaddition reactions^{14,15}. However, the arylation of amines has not been widely studied due to the difficulty in generating arynes under convenient reaction conditions.

Recently, we reported reactions of 2-alkenyl- and 2-hydrazinyl-1-methylpyrroles with aryne generated from silylaryl triflate under very mild reaction conditions provide excellent yields of arylated products, while tolerating many functional groups¹⁶. Here in, we wish to report the full details of this very efficient arylation procedure and our studies on the addition to silylaryl triflate.

EXPERIMENTAL

General procedure for the mono-N-arylation of aromatic amines. To a solution of MeCN (5 mL), aromatic amine (0.50 mmol) and silylaryl triflate (0.50 mmol) was added CsF (1 mmol). The reaction mixture was allowed to stir at room temperature and monitored by TLC to establish completion of the reaction. The resulting solution was washed with brine (20 mL) and extracted with diethyl ether (20 mL). The combined ether fractions were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the desired product. Diphenylamine (Table-1, entry 1). Purification by flash chromatography (30:1, hexane/EtOAc) afforded the indicated

compound (38 mg) in a 92 % yield as a white solid: m.p. 49–50 °C (lit.¹⁷ mp 50–52 °C). The ¹H and ¹³C NMR spectra match the literature data¹⁸.

General procedure for the amines, 2,5-dimethoxytetrahydrofuran, 1,3-acetone carboxylic acid and silylaryl triflate. To a solution of MeCN (5 mL), amines (0.50 mmol), silylaryl triflate (0.50 mmol), 2,5-dimethoxytetrahydrofuran (0.50 mmol) and 1,3-acetone carboxylic acid (0.50 mmol) was added CsF (1 mmol). The reaction mixture was allowed to stir at room temperature and monitored by TLC to establish completion of the reaction. The resulting solution was washed with brine (20 mL) and extracted with diethyl ether (20 mL).

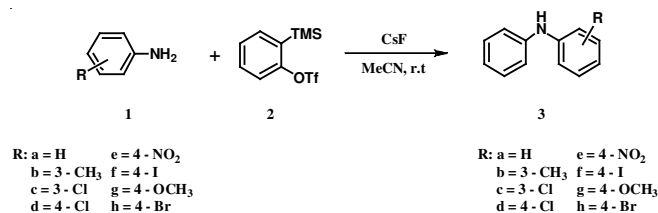
The combined ethereal fractions were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the desired product.

RESULTS AND DISCUSSION

Preparation of the aryne precursor: The aryne **2** were selected as substrate for our experiments. Aryne precursor **2** was selected as the simplest and most readily available aryne to study the scope of this chemistry. The synthesis of silylaryl triflate **2** has already been reported.

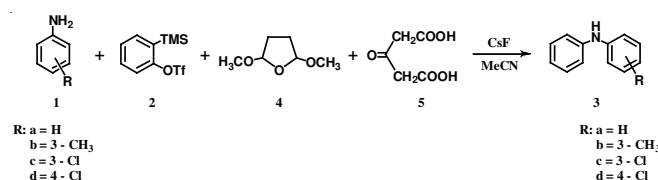
N-Arylation of aromatic amines: Our initial studies focused on achieving optimal reaction conditions for the N-arylated product using aniline and silylaryl triflate **1** as the model system. We first allowed 2-(trimethylsilyl)phenyl triflate **2** to react with 1 equiv of CsF and 1.2 equiv of aniline in MeCN at room temperature for 20 h. Diphenylamine was obtained in an 90.2 % yield and only a trace of triphenylamine was isolated. After trying several reactions, we found that THF was also a good solvent for the N-arylation of aniline and CsF can be replaced by *n*-Bu₄NF (TBAF). Although the reaction time can be dramatically decreased to 0.5 h when *n*Bu₄NF is allowed to react with the silylaryl triflate **2** to generate benzyne, the yield is a little lower. The optimal reaction conditions thus far developed employ 0.50 mmol of aniline, 1.1 equiv of silylaryl triflate **2** and 0.15 g of CsF in MeCN (5 mL) at room

temperature for 24 h. Diphenylamine was obtained in a 90.2 % yield (**Scheme-I**) (Table-1, entry 1).



Scheme-I

We next studied the scope of this methodology by allowing a wide variety of aromatic amines to react with the silylaryl triflates **2**¹⁹. The results are summarized in Table-1. Aniline itself and aniline with electron-donating and withdrawing groups (Table-1, entries 1 and 3–8), such as nitro, iodo, bromo and methoxy groups, all react well with silylaryl triflate **2** and CsF to afford excellent yields of the desired phenyl-substituted products. It is noteworthy that haloanilines also react with silylaryl triflate **2** to generate the desired halo-substituted products in excellent yields (Table-1). Halides, which are unlikely to survive under the Pd-mediated amination reaction conditions are readily accommodated by our reaction conditions. In order to synthesize biologically active compounds, when the reaction of amines (aniline, *m*-toluidine, 3-chloroaniline, 4-chloroaniline), 2,5-dimethoxytetrahydrofuran, 1,3-acetone dicarboxylic acid and silylaryl triflate **2** (Tables 2 and 3), good yields of the N-arylated products are still obtained (**Schemes II** and **III**).



Scheme-II

TABLE-1
FACILE N-ARYLATION OF AROMATIC AMINES

Entry	Amine 1	Silylaryl triflate (mmol) 2	CsF (mmol)	Time (h)	Product 3	Isolated yield (%)
1	a	0.5	1	24		90.2
2	b	0.5	1	24		92.1
3	c	0.5	1	24		84.3
4	d	0.5	1	24		86.6
5	e	0.5	1	24		85.7
6	f	0.5	1	24		92.2
7	g	0.5	1	24		89.5
8	h	0.5	1	24		91.1

^aAll reactions were run under the following reaction conditions, under otherwise specified: 0.50 mmol of amine and the indicated amount of silylaryl triflate and CsF were stirred in 5 mL of MeCN at room temperature. Only monoarylated product was obtained.

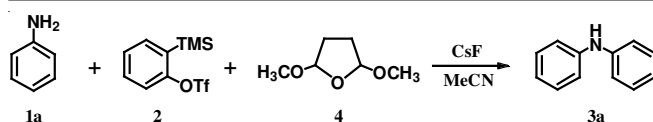


TABLE-2
N-ARYLATION OF AROMATIC AMINES BY
USING 2,3-DIMETHOXYTETRAHYDROFURAN **4**
AND 1,3-ACETONEDICARBOXYLIC
ACID **5** WITH *o*-SILYLARYL TRIFLATE **2**

Entry	Amine	Starting materials	CsF (mmol)	Product	Isolated yield (%)
1	1a	4 + 5	1	3a	87.6
2	1b	4 + 5	1	3b	90.3
3	1c	4 + 5	1	3c	85.7
4	1d	4 + 5	1	3d	83.9

TABLE-3
N-ARYLATION OF AROMATIC AMINES
BY USING 2,5-DIMETHOXYTETRAHYDROFURAN
WITH *o*-SILYLARYL TRIFLATE **2**

Entry	Amine	Starting materials	CsF (mmol)	Product	Isolated yield (%)
1	1a	4	1	3a	89.8

Substantially we reported^{20,21} the synthesis of N-substituted pyrroles and nortropinones in the reaction of amines with 2,5-dimethoxytetrahydrofuran and 1,3-acetone dicarboxylic acid. When the reaction of aniline, 2,5-dimethoxytetrahydrofuran and silylaryl triflate **2** with CsF in MeCN executed, good yield of diphenylamine as a N-arylated product is still obtained. But synthesis of N-substituted pyrrole and nortropinone did not occur (Tables 2 and 3).

In summary, from Table-1, one can see that almost all aromatic amines react well with silylaryl triflate and CsF under very mild reaction conditions to afford good to excellent yields of the desired products. It should be pointed out that a variety of other functional groups, including halide should be readily tolerated under present reaction conditions.

Conclusion

An efficient, mild, transition-metal-free method is developed for the N-arylation of amines. Monoarylated amines can easily be obtained from primary amines by simply controlling the ratio of the reactants. A variety of functional groups are compatible with the reaction conditions, including nitro, iodo, bromo and methoxy groups. It is also shown that halides, which are not compatible with Pd-mediated arylation procedures, readily tolerate the reaction conditions.

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