Tetrahedron Letters 52 (2011) 5847–5850

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A facile *N*-arylation of acetanilides with arynes

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ARTICLE INFO

Article history:
Received 20 July 2011
Revised 22 August 2011
Accepted 24 August 2011
Available online 31 August 2011

Keywords:
Arynes
N-Arylation
Acetanilides
ortho-Silylaryl triflates
Tetrabutylammonium triphenyldifluorosilicate

ABSTRACT

An efficient, mild and transition-metal-free method for the *N*-arylation of acetanilides, leading to a range of unsymmetrical diarylamine products is reported. Reactions of *ortho*-silylaryl triflates with acetanilides in the presence of tetrabutylammonium triphenyldifluorosilicate (TBAT) in toluene afforded the desired products in good to excellent yields. Regioselectivity was also observed when unsymmetrical aryne precursors were used.

The development of efficient methods for the synthesis of *N*-aryl amides has been an active area in organic chemistry due to the abundance of amide moieties in biologically active molecules.[1] The Goldberg reaction (copper-mediated *N*-arylation of amides with aryl halides in the presence of CuI and K_2CO_3) was the first method utilized to synthesize this class of compounds.[2] However, high temperatures (>200 °C) and often greater than stoichiometric amounts of copper salts or copper metal were necessary to achieve moderate yields of the cross-coupled products. More recently, significant advances have been made in this area utilizing copper catalysts with 1,2-diamine, diamine, β-ketoester, amino acid, and hydrazone ligands.[3] However, relatively high temperatures (>100 °C) are still required and undesired reactivity with some ligands still pose limitations to the definition of generalized conditions. To overcome these difficulties, palladium-catalyzed methods were developed, which use sterically hindered phosphine ligands to couple aryl halides with amides under relatively mild conditions.[4] However, the need to optimize the matching of catalyst, ligand, solvent, and base to the appropriate substrate pair is often required, and the sensitivity of some reagents to air and moisture limits the scope of this process.

Since Kobayashi reported a mild method for the in situ preparation of benzyne,[5] much attention has been paid to applying *ortho*-silylaryl triflates as benzyne precursors to a variety of synthetically useful transformations.[6] In particular, arylation of amines, sulfonamides, and carboxylic acids under very mild conditions were intensively investigated by the Larock group.[7] However, *N*-arylation of simple amides remains problematic under these conditions probably due to the fact that simple primary amides are often not nucleophilic enough to directly attack benzyne.[7] In a recent communication, Greaney[6a] described an *N*-arylation of *N*-phenylpropionamide in the context of a deuterium labeling study, which is the only literature example of an acetanilide substrate undergoing an intermolecular benzyne mediated *N*-arylation reaction reported to date.[8] Therefore, we felt that a simple and general procedure to generate *N*-arylation products from simple acetanilides under mild conditions would be desirable. Herein, we describe the development of an efficient *N*-arylation of acetanilides from arynes generated in situ along with the scope and limitations of this transformation.

Our initial study focused on finding optimal conditions for the *N*-arylation of phenyl acetamide (**1a**, Table 1). To our initial disappointment, the reaction of **1a** with benzyne precursor **2a** in the presence of cesium fluoride in toluene at 50 °C did not afford any desired product **3a** (Entry 1). In addition, under Larock's conditions (cesium fluoride in acetonitrile), only a trace amount of product was observed (Entry 2). After several unsuccessful attempts utilizing various solvents (Entries 3–5), the combination of the alternative fluoride source tetrabutylammonium triphenyldifluorosilicate (TBAT) in toluene, was the key to reproducibly achieve this reaction in good yields (Entries 6–8). When 1.5 equiv of **2a** and 2 equiv of TBAT were used, the desired product was isolated in 68% yield (Entry 6). Increasing the amount of TBAT to 3 equiv did not lead to any improvement (Entry 7); however, higher amounts of both TBAT and **2a** afforded an 85% isolated yield of **3a** (Entry 8).

With the optimized conditions in hand, the scope of this method was studied by reacting a variety of acetanilides with *ortho*-silylaryl

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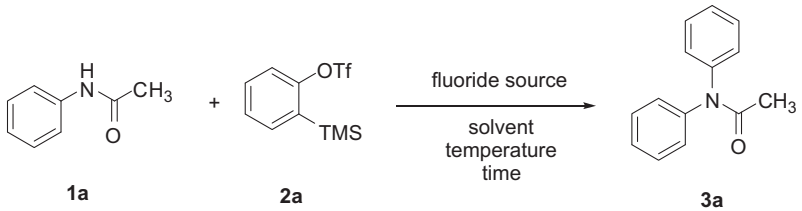
doi:10.1016/j.tetlet.2011.08.146

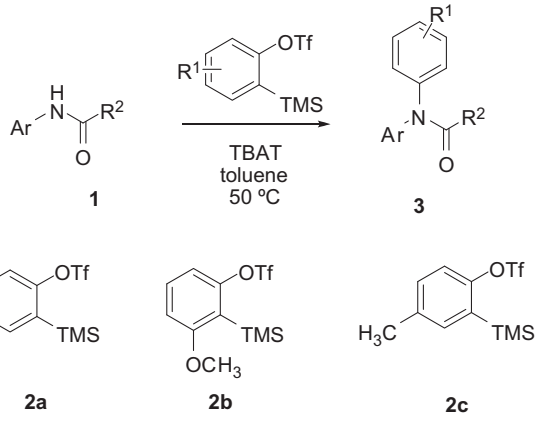
Table 1
Optimization of reaction conditions



Entry	**2a** (equiv)	Fluoride source (equiv)	Solvent	Temperature (°C)	Time (h)	Yield (%)
1	1.5	CsF (3)	Toluene	50	12	0
2	1.2	CsF (2)	MeCN	rt	12	Trace
3	1.5	TBAT (2)	MeCN	50	20	Trace
4	1.5	TBAT (2)	DME	50	24	Trace
5	1.5	TBAT (2)	THF	50	24	Trace
6	1.5	TBAT (2)	Toluene	50	24	68[a]
7	1.5	TBAT (3)	Toluene	50	24	68[a]
8	2	TBAT (4)	Toluene	50	18	85[a]

[a] Isolated yield.

Table 2
Facile *N*-arylation of carboxamides[a]



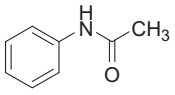
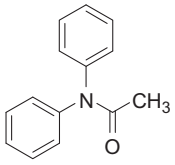
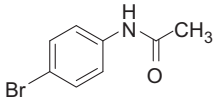
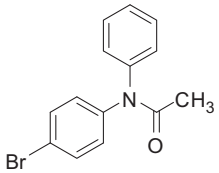
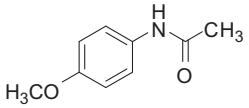
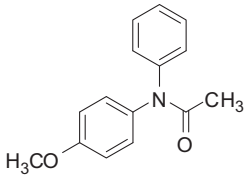
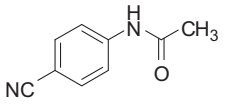
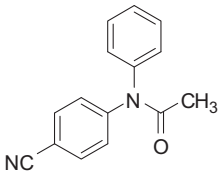
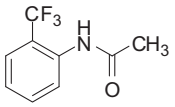
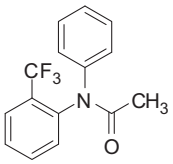
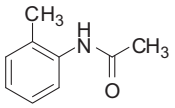
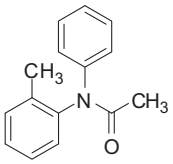
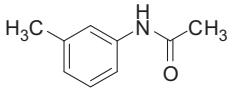
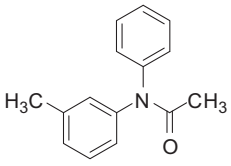
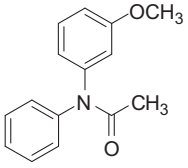
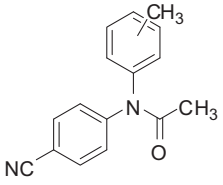
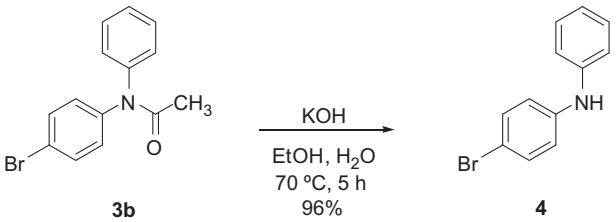
Entry	Amide	Silylaryl triflate	Product	Time (h)	Isolated yield
1	 **1a**	**2a**	 **3a**	18	85%
2	 **1b**	**2a**	 **3b**	18	81%
3	 **1c**	**2a**	 **3c**	24	72%

Table 2 (*continued*)

Entry	Amide	Silylaryl triflate	Product	Time (h)	Isolated yield
4	 **1d**	**2a**	 **3d**	5	85%
5	 **1e**	**2a**	 **3e**	12	57%
6	 **1f**	**2a**	 **3f**	7	66%
7	 **1g**	**2a**	 **3g**	20	78%
8	**1a**	**2b**	 **3h**	28	70%
9	**1d**	**2c**	 **3i**	24	83% *meta*:para 1.2:1

[a] *Reaction conditions:* 0.25 mmol of amide **1**, 0.50 mmol of aryne precursor **2**, 1.00 mmol of TBAT in 3 mL of toluene at 50 °C, also see Ref. 9.

triflates **2a**–**2c**, the results of which are summarized in Table 2.[9] Acetanilides of varying electronic characteristics, both electron donating or withdrawing reacted very well with silylaryl triflate **2a** to afford the desired products in good yields, with electron poor acetanilides undergoing conversion much faster (Entries 4 and 5). It is noteworthy that a bromo substituent (Entry 2), which is unlikely to be tolerated under palladium-catalyzed coupling conditions, was readily tolerated under our much milder protocol. The reaction appears to be sensitive to steric hindrance with Entries 5 and 6 showing only moderate yields for *ortho*-substituted acetanilide substrates. The regiochemistry of the arylation with unsymmetrical arynes was also investigated. The reaction of methoxy substituted silylaryl triflate **2b** clearly generated a single regioisomer **3h** as the only product (Entry 8), which can be readily explained by steric and electronic effects.[7a,10] However, when the electronically neutral aryl triflate **2c** was used, a mixture of 1.2:1 *meta*- and *para*-substituted regioisomers (determined by ^{1}H NMR) was isolated (Entry 9). This is not unexpected considering the distance of the methyl sub-



3b **4**

Scheme 1.

stituent from the in situ generated benzyne reacting center. It should be pointed out that our attempts to extend this method to additional substrates such as indolin-2-one were unsuccessful, which we attributed to the complications of steric hindrance. We also found that acetamide and benzamide failed to provide the corresponding *N*-aryl products using this method, which further suggests that primary carboxamides are not sufficiently nucleophilic enough to react with benzyne generated under these conditions.

The removal of the acetyl group from the nitrogen of *N*-aryl acetanilide product **3b** was also performed as proof of principle for the utility of the protocol (Scheme 1). As expected, a diarylamine product **4** was isolated in high yield, providing this unsymmetrical diarylamine in a manner that should find its applicability as a general method.

In summary, we developed an efficient, mild and transition-metal-free method for the *N*-arylation of acetanilides that is tolerant of a range of functional groups. This chemistry offers a convenient and mild alternative method to metal-catalyzed protocols to afford *N*-arylation products. Due to relative ease of removal of acetyl group on nitrogen,[11] this method should serve as a useful approach to the preparation of many unsymmetrical diarylamines.[12]

Acknowledgments

Drs. R. Jason Herr and Keith D. Barnes are gratefully acknowledged for helpful discussions and suggestions during the course of this study.

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9. Typical procedure for the preparation of *N*,*N*-diphenylacetamide (**3a**): A mixture of **1a** (34 mg, 0.250 mmol), **2a** (149 mg, 0.500 mmol) and TBAT (540 mg, 1.00 mmol) in toluene (3 mL) was stirred at 50 °C for 18 h. After this time, the reaction mixture was cooled to ambient temperature and concentrated under reduced pressure. The residue obtained was purified by flash chromatography (silica, heptane to 2:3 ethyl acetate/heptane) to afford **3a** (45 mg, 85%) as an off-white solid: mp 73–75 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.41–7.39 (m, 10H), 1.93 (s, 3H); 13C NMR (75 MHz, DMSO-d_6) δ 169.2, 143.2, 134.5, 129.2, 127.7, 23.3; ESI MS *m*/*z* 212 $[M+H]^+$; HRMS ESI *m*/*z* $[M+H]^+$ calcd for $C_{14}H_{14}NO$: 212.1075; found: 202.1084.
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