Tetrahedron 70 (2014) 6879–6884

Contents lists available at ScienceDirect

Tetrahedron

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

Highly selective acetoxylation of sulfonamides via using phenyliodine(III) diacetate

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ARTICLE INFO

Article history:
Received 25 April 2014
Received in revised form 27 June 2014
Accepted 2 July 2014
Available online 15 July 2014

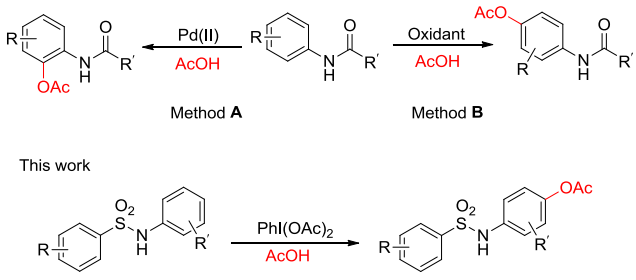
Keywords:
para-Acetoxylation
ortho-Acetoxylation
N-Phenylbenzenesulfonamides

ABSTRACT

A highly efficient acetoxylation reaction of *N*-aryl-arylsulfonamides has been developed, presumably proceeding via the selective functionalization of *N*-aryl C–H bonds. A stoichiometric amount of $PhI(OAc)_2$ was generally employed as the oxidation reagent, and various *para*-acetoxylated sulfonamide derivatives had been generated in excellent yields. This chemistry endowed an economic synthesis of valuable acetoxylated sulfonamides through direct C–O bond formation processes.

1. Introduction

Selective oxygenation of aromatic compounds remained a difficult challenge in organic synthesis, and the development of effective methodologies has attracted the interest of many organic chemists.[1] Various methods featuring direct functionalization of C–H bonds of arenes to form carbon–carbon or carbon–heteroatom bonds have been explored, yet mostly mediated by transition-metal catalysts.[2,3] Particularly, the construction of C–O bond is of extraordinary importance, presumably due to its abundance in biologically-interesting compounds and pharmaceutical agents, as demonstrated by Sanford and others.[4] However, a vast majority of the C–O bond formation reactions reported in the literature utilizes transition-metal catalysts, and the examples involving transition-metal-free processes were fairly rare.[5,6] On the other hand, these C–O coupling reactions were mainly employed to afford acetoxy- or alkoxy-substituted anilides, and they could be briefly classified into two representative categories: (1) transition-metal-catalyzed C–O coupling reactions (Scheme 1, method A), and (2) transition-metal-free C–O bond formation methodologies (Scheme 1, method B).[6,7] Recently, hypervalent iodine compounds have been extensively investigated in a large number of oxidative C–O coupling reactions, especially in the acetoxylation of anilides.[6h] In contrast to the highly toxic heavy metal oxidants like Pb(II), Tl(III) and Hg(II), hypervalent iodine(III) reagents appear to possess several advantages, such as low toxicity, mild oxidation abilities, excellent availability and ease of handling, therefore, they have been found broad applications in organic syntheses.[8] Surprisingly, method involving selective C–O bond formation processes have not been developed for the syntheses of sulfonamide derivatives. Because substituted sulfonamides are pivotal building blocks for pharmaceuticals and bioactive compounds, we aim to develop an efficient synthesis of such compounds using oxygen nucleophiles.[9] Herein we report a novel transition-metal-free synthesis of *N*-aryl-arylsulfonamide derivatives, which presumably proceeds via the direct oxidative functionalization of sp^2 C–H bonds with hypervalent iodine reagents. Plus, this chemistry does not require toxic reagents or harsh conditions, affording an operationally-friendly method for academic and industrial laboratories.



Scheme 1. Acetoxylation of anilines.

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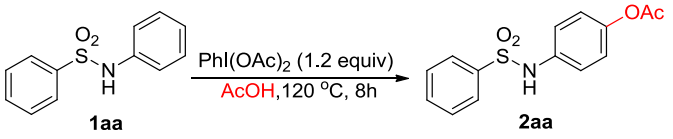
http://dx.doi.org/10.1016/j.tet.2014.07.007
0040-4020/

2. Results and discussion

2.1. Optimization studies

In an effort to identify suitable reaction conditions, the reaction of commercially available benzenesulfonyl chloride and aniline was conducted to afford *N*-phenylbenzenesulfonamide (**1aa**), which was subsequently treated with various oxidants in different solvents. In our initial work, sulfonamide **1aa** was allowed to react with 1.2 equiv of phenyliodine(III) bis(trifluoroacetate) (PIFA) in acetic acid for 8 h, affording a 52% yield of the *para*-acetoxylated product **2aa** (Table 1, entry1). Surprisingly, when phenyliodine(III) diacetate (PIDA) was used as the oxidant for this transformation, a 87% yield of the desired product was obtained after flash chromatography (entry 2). On the contrary, four other oxidants had been closely examined in this chemistry and none of them were effective (entries 3–6). Those results indicated that the oxidation reagent $PhI(OAc)_2$ was crucial for the success of this remarkable C–O bond formation process. We next studied the effect of reaction temperature, and we found a lower temperature would dramatically decrease the reaction efficiency (entries 7 and 8). As expected, no formation of **2aa** was evident when the reaction was conducted at room temperature (entry 9). In order to examine the effect of solvents, CF_3COOH, PivOH and Ac_2O were consecutively employed in this transformation. However, starting material **1aa** was completely decomposed in these solvents and no desired product was formed (entries 10–12). Other solvents such as toluene, dioxane or acetonitrile were also examined and the results were inferior (entries13–15). To that end, it was decided that the 'optimal' conditions for this transformation was the utilization of 1.2 equiv of $PhI(OAc)_2$ in acetic acid at 120 °C for 8 h.

Table 1
Optimization of reaction conditions[a]



Entry	Oxidant	Solvent	Temperature (°C)	Yield[b]
1	$PhI(OCOCF_3)_2$	AcOH	120	52%
2	**$PhI(OAc)_2$**	**AcOH**	**120**	**87%**
3	^tBuOOH	AcOH	120	n.r.[c]
4	H_2O_2	AcOH	120	n.r.[c]
5	K_2SO_4	AcOH	120	n.r.[c]
6	O_2	AcOH	120	n.r.[c]
7	$PhI(OAc)_2$	AcOH	90	65%
8	$PhI(OAc)_2$	AcOH	60	30%
9	$PhI(OAc)_2$	AcOH	30	n.r.[c]
10	$PhI(OAc)_2$	TFA	120	—[d]
11	$PhI(OAc)_2$	PivOH	120	—[d]
12	$PhI(OAc)_2$	Ac_2O	120	—[d]
13	$PhI(OAc)_2$	Toluene	120	n.r.[c]
14	$PhI(OAc)_2$	Dioxane	120	n.r.[c]
15	$PhI(OAc)_2$	CH_3CN	120	n.r.[c]

The bold in Table 1 is the optimal condition.
[a] Reactions were carried out on a 0.5 mmol scale in 3.0 mL of solvent with 1.0 equiv of 1a, 1.2 equiv of oxidant at 120 °C for 8 h.
[b] Isolated yield after column chromatography.
[c] n.r.=no reaction.
[d] Decomposed.

2.2. Scope and limitations

With the best reaction conditions in hand, we next explored the scope and limitations of this chemistry, and the results were summarized in Scheme 2. When *N*-phenyl-arylsulfonamides **1** bearing different substituents on the arylsulfonyl moieties were subjected to the 'optimal' reaction conditions, moderate to excellent yields of *para*-acetoxylated sulfonamide products were obtained (**2aa**–**ah**). Specifically, the reaction of *N*-phenyl-benzenesulfonamide afforded an 87% yield of the desired product (**2aa**). Substrates bearing electron-donating groups on the *para*-positions of arylsulfonyl motifs worked well under the standard conditions as well (**2ab** and **2ac**). Interestingly, when halogen-substituted arylsulfonamides were employed in this transformation, high yields of the corresponding acetoxylated products were also obtained (**2ad** and **2ae**). In addition, strong electron-withdrawing groups like NO_2 could also be tolerated, and 78–81% yields of the desired products were isolated after flash chromatography (**2af**–**ah**). These results indicated that the electronic nature of substituents on the arylsulfonyl moieties generally would not affect the reaction efficiency.

To our delight, when sulfonamides bearing functionalities on the *N*-phenyl motifs were examined under the standard conditions, a diverse set of *para*-acetoxylated products were obtained in moderate to excellent yields (**2ba**–**bk**). For instance, *N*-aryl-benzenesulfonamide possessing bromo group on the aniline rings afforded 83–88% yields of the corresponding products (**2ba**–**bc**). Similarly, the acetoxylation reactions of nitro substituted analogs afforded 80–85% yields of the sulfonamides (**2bd**–**bf**). On the other hand, when substrates bearing hydrogen, chloro, and bromo groups on arylsulfonyl moieties were allowed to react under the same conditions, moderate to excellent yields of *para*-acetoxylated products were obtained (**2bg**–**bi**). Encouraged by those results, *N*-(2,6-dimethyl-phenyl)-4-nitro-benzenesulfonamide was prepared and subject to the previously described conditions, affording a 92% yield of the sulfonamide product (**2bj**). However, the acetoxylation reaction of 4-methyl-*N*-(2-fluoro-6-methyl-phenyl)-benzenesulfonamide only produced a 73% yield of the desired sulfonamide **2bk**.

We next examined the reaction efficiency of additional substrates possessing electron-donating groups or electron-withdrawing groups on the *meta*-position of the aniline arene, and it was found that respectful yields of the desired products were usually obtained. Specifically, the acetoxylation reactions of substrates bearing methyl and chloro groups afforded good yields of the corresponding sulfonamides (**2ca** and **2cb**), whereas the methyl-containing substrates afforded 78–90% yields of the desired products (**2cc**–**cf**).

To our surprise, further examination of the scope revealed that a wide variety of *para*-substituted sulfonamides underwent *ortho*-acetoxylation in good yields (**2da**–**de**). Selective mono-acetoxylation and *ortho*-selectivity with respect to the amino group was observed in *para*-substituted substrates, whether the electron-donating (**2da**–**dd**) or electron-withdrawing (**2de**) groups on the substitution.

2.3. Mechanistic considerations

Given the fact that a number of direct acetoxylation reactions of anilides have been reported,[6g,h] and electrophilic substitution processes are generally involved, we propose a similar mechanistic pathway for the synthesis of compound **2**, as shown in Scheme 3.[6a,b,d,h] Theoretically, the reaction of arylsulfonamides **1** with iodine(III) electrophile should afford a key intermediate **A**, which subsequently undergoes a N–I bond cleavage reaction to generate the nitrenium cation **B**, accompanied with the loss of one molecule of iodobenzene. Consequently, intermediate **B** should undergo a charge delocalization process to afford more stable intermediate **C**, which would readily react with AcOH and eventually lead to the formation of *para*-acetoxylated arylsulfonamides **2**. On the other hand, when the substituents on the *para*-position of aniline ring, nitrenium ion B changed into charge delocalized intermediate D and, which react with acetic acid afforded corresponding *ortho*-acetoxylated products 3.