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Palladium-catalyzed direct arylation of pyridine *N*-oxide with 2-bromoacetanilides. Synthesis of benzisoxazolo[2,3-*a*]pyridinium tetrafluoroborates

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Abstract

The synthesis of a variety of novel benzisoxazolo[2,3-*a*]pyridinium tetrafluoroborates is described. These compounds are conveniently prepared from pyridine *N*-oxide via a microwave-promoted palladium-catalyzed direct arylation of pyridine *N*-oxide with 2-bromoacetanilides to give 2-(2-acetamidoaryl)pyridine *N*-oxides, followed by hydrolysis, diazotization and intramolecular displacement of nitrogen which affords the target benzisoxazolo[2,3-*a*]pyridinium tetrafluoroborates.

Keywords

Benzisoxazolo[2,3-*a*]pyridinium; Palladium-catalyzed direct arylation; Pyridine *N*-oxide; Microwave synthesis

Introduction

The benzo[4,5]furopyridine substructure (Figure 1) is a common motif in a variety of biologically active compounds. Substances containing this structural unit have been shown to exhibit activity against cancer,^{1,2} tuberculosis,³ osteoporosis,⁴ and HIV.⁵

Although considerable effort has been directed toward the synthesis of these compounds,^{6–8} the related ring system benzisoxazolo[2,3-*a*]pyridinium (**1**, Figure 2) has not attracted as much attention; in fact only two examples have been reported to date.⁹

Abramovitch and Inbasekaran described the synthesis of **1** (R = H) from 2-(2-aminophenyl)pyridine *N*-oxide by conversion to the diazonium salt followed by intramolecular displacement of nitrogen in refluxing acetonitrile (Scheme 1); this compound was then nitrated to give **1** (R = NO₂). A related benzisoxazolo[2,3-*b*]isoquinolinium

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Supplementary data

Supplementary data (experimental procedures, detailed product characterization data, compound spectra) associated with this Letter can be found in the online version at (**Editor: Please insert DOI here**).

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tetrafluoroborate was prepared by Timári et al. in a similar manner.¹⁰ Given the biological activity of the benzo[4,5]furopyridines and that the similar 2-arylisoxazolo[2,3-*a*]pyridinium salts¹¹ have been reported to be useful for the treatment of inflammation and gastric hyperacidity,¹² we became interested in developing a general synthesis of compounds of type **1** to facilitate any future investigations of their pharmacological properties.

We felt that the Abramovitch strategy (Scheme 1) involving ring closure of a diazonium salt derived from an appropriate 2-(2-aminoaryl)pyridine *N*-oxide was the simplest approach to the desired compound **1**, therefore we sought to synthesize several differently substituted 2-(2-aminoaryl)pyridine *N*-oxides, from which we could carry out the diazotization and attempt ring closure to **1**. A search of the literature uncovered very few approaches to the required 2-(2-aminoaryl)pyridine *N*-oxides; most resulted from oxidation of the corresponding 2-(2-aminoaryl)pyridine.¹³ These compounds were prepared either by reduction of the corresponding 2-(2-nitroaryl)pyridine (prepared by reaction of pyridine with an *o*-nitroaryldiazonium salt^{14,15}), by palladium-catalyzed cross-coupling of a (2-aminophenyl)boronate ester with a 2-halopyridine,¹⁶ or by palladium-catalyzed coupling of 2-pyridylzinc bromide with a 2-haloaniline.¹⁷ Since many of these existing methods suffer from low yields or limited scope, we decided to explore the palladium-catalyzed direct arylation of pyridine *N*-oxide (**2**) with an appropriate 2-bromoacetanilide (**3**) using the method developed by Fagnou.^{18,19} Although this protocol had not yet been applied using 2-bromoacetanilides as coupling partners, we believed it would provide a simple route to a wide variety of acetylated 2-(2-aminoaryl)pyridine *N*-oxides (**4**). Subsequent hydrolysis, diazotization to **5** and ring closure would then afford **1** (Scheme 2).

We can now report that the pathway described in Scheme 2 is a viable route to a variety of benzisoxazolo[2,3-*a*]pyridinium tetrafluoroborates (**1**). In this Letter, we describe the results of our study.

Results and discussion

We began our study by examining the direct arylation of pyridine *N*-oxide (**2**) with 2'-bromo-4'-methylacetanilide (**3a**). Initially, we found that microwave heating of a mixture of **2** (4 equiv) with **3a** in the presence of palladium acetate (5 mol %), tri-*tert*-butylphosphonium tetrafluoroborate (15 mol %), and potassium carbonate (2 equiv) in toluene to 140 °C using no special oxygen- or water-exclusion techniques gave compound **4a** in 35% yield after chromatography (average of 3 runs).²⁰ The balance was mainly 4'-methylacetanilide, resulting from protidebromination of **3a**, plus a small amount (~5%) of **3a**. Screening of various ligands using yields determined by ¹H-NMR revealed that di-*tert*-butylmethylphosphonium tetrafluoroborate gave the best results among the ligands studied (80% yield, Scheme 3), therefore it was used for all further direct arylations. The other phosphonium salts as well as the *N*-heterocyclic carbene precursor 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazolium tetrafluoroborate (H₂IPr-HBF₄) were not as effective. Under these conditions, **4a** was produced in an average yield of 65% after chromatographic purification.

We were able to prepare several examples of **4** containing both electron-withdrawing and electron-donating substituents using this protocol; the results are shown in Table 1. Small-scale runs (0.6 mmol **3**) were performed using a 10-mL vessel and were usually complete within 1 hr, while larger scale runs (3.0 mmol **3**), carried out in an 80-mL vessel, generally required about 3 hr for complete reaction. The direct arylation proceeded smoothly in most cases to give synthetically useful yields of **4**; the exception involved the reaction of 2'-bromo-4'-chloroacetanilide (**3h**, entry 8), which gave virtually no **4h** under the standard conditions. Fortunately, lowering the reaction temperature from 140 °C to 110 °C allowed

us to overcome this limitation and as a result, **4h** could be synthesized in a 51% yield. We speculate that side reactions involving oxidative addition to the carbon-chlorine bond to the palladium catalyst were occurring at 140 °C, and that these were minimized at the lower temperature.

The observation that the direct arylation of **3h** could occur at the lower temperature (i. e. at the boiling point of the solvent toluene) suggested the possibility that the reaction may give an acceptable yield in a reasonable amount of time under standard reflux conditions without requiring microwave heating. We therefore conducted direct arylations of both **3a** and **3h** in refluxing toluene using conventional (oil-bath) heating and determined the product yields by ¹H-NMR. Under these conditions, **4a** was produced in 62% yield from **3a** after a 3 hr reflux period. No unreacted **3a** was detected; the remainder was 4'-methylacetanilide (debrominated **3a**). Although this is a reasonable yield, it is lower than the 80% yield we found during our ligand screening experiments (Scheme 3). Under similar conditions, however, **3h** gave only a 20% yield of **4h**. In this case, some unreacted **3h** was detected but the major product appeared to be the debrominated starting material 4'-chloroacetanilide. Based on these results, it seems that microwave heating is necessary to consistently achieve the product yields reported in Table 1.²¹

Having a method to prepare the required starting material for the cyclization in hand, we turned our attention to the hydrolysis, diazotization, and cyclization. Initial experiments employing **4a** indicated that both the hydrolysis (in refluxing aqueous HCl) and diazotization (NaNO₂/HCl) proceeded smoothly as expected, but in our hands isolation of the diazonium salt by precipitation as the solid tetrafluoroborate salt proved difficult. This problem was solved by hydrolyzing **4a** in aqueous HBF₄ to the anilinium tetrafluoroborate which, after removal of the water and replacement with acetonitrile, could be diazotized with *tert*-butyl nitrite. Cyclization to compound **1a** occurred smoothly in the same solution by heating it to reflux for a short period of time. Using this protocol, hydrolysis, diazotization and cyclization of **4** proceeded efficiently in all cases. The results are shown in Table 2.

Summary

In summary, we have shown that a variety of novel benzisoxazolo[2,3-*a*]pyridinium tetrafluoroborates (**1**) can be conveniently prepared from pyridine *N*-oxide, which may facilitate investigations into the biological activity of these compounds. In doing so, we have also expanded the scope of the palladium-catalyzed direct arylation of pyridine *N*-oxide to include 2-bromoacetanilides as coupling partners to give the previously unknown 2-(2-acetamidoaryl)pyridine *N*-oxides (**4**). In addition, we have shown that the direct arylation gives **4** in synthetically useful yields using microwave heating without any special water- or oxygen-exclusion techniques. Further application of this strategy to the synthesis of other novel heterocyclic systems is being investigated in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Benzo[4,5]fuopyridines.

Figure 2.
Benzisoxazolo[2,3-*a*]pyridinium tetrafluoroborates.

Scheme 1.
Abramovitch synthesis of **1**.⁹

Scheme 2.
Proposed general route to **1**.

Ligand	% Yield (NMR)
$t\text{Bu}_3\text{P-HBF}_4$	53
$t\text{Bu}_2\text{MeP-HBF}_4$	80
$\text{Cy}_3\text{P-HBF}_4$	23
$\text{H}_2\text{IPr-HBF}_4$	35

Scheme 3.
Direct arylation of **2** with **3a**.

Table 1

Preparation of **4**^a

Entry	Acetanilide (3)	Product (4)	% Yield ^b
1			65
2			65
3			76
4			55
5			60
6			70
7			64

^aExperiments carried out with **2** (4 equiv), **3** (1 equiv), Pd(OAc)₂ (5 mol %), ^tBu₂MeP-HBF₄ (15 mol %), K₂CO₃ (2 equiv) in toluene (3.3 mL/mmol **3**). The mixture was heated to 140 °C in a CEM/Discover Benchmate microwave reactor.

^bIsolated yields; average of at least 2 runs.

^cHeated to 110 °C.

Table 2Preparation of benzisoxazolo[2,3-*a*]pyridinium tetrafluoroborates (**1**)^a

Entry	Acetanilide (4)	Product (1)	% Yield ^b
1	4a	 1a	72
2	4b	 1b	77
3	4c	 1c	83
4	4d	 1d	79
5	4e	 1e	80
6	4f	 1f	71
7	4g	 1g	76

^aHydrolysis: **4** (1.0 mmol), HBF₄ (50% aqueous solution, 1.2 mmol), water (1 mL), were refluxed until hydrolysis was complete. Diazotization/cyclization: the preceding mixture was evaporated *in vacuo* and dissolved in CH₃CN (8 mL). *t*BuONO (1.2 mmol) was added. Mixture was stirred 1 hr at RT, then heated to reflux.

^bIsolated yields; average of at least 2 runs.