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Copper-mediated N-arylation of methyl 2-aminothiophene-3-carboxylate with organoboron reagents

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ABSTRACT

A practical protocol for the synthesis of *N*-arylated methyl 2-aminothiophene-3-carboxylate has been developed via Chan–Lam cross-coupling. The desired products were synthesized by cross-coupling of methyl 2-aminothiophene-3-carboxylate with both arylboronic acids and potassium aryltrifluoroborate salts in moderate to good yields. A broad range of functional groups was well tolerated.

Introduction

Thiophene-containing compounds have attracted much attention because of their intrinsic electronic properties, which make them important in light-emitting diodes, field effect transistors, organic solar cells, and photovoltaic devices.[1–5] Thiophene derivatives have also shown versatile pharmacological activities.[6–14] In particular, substituted aminothiophenes, including 2-aminothiophene-3-carboxylate derivatives, appear to be of interest in medicinal chemistry and are represented in several classes of biologically active molecules.[15–17]

Traditionally, N-arylation of these systems was achieved through nucleophilic aromatic substitution of the amines with aryl halides, although activated substrates and strong conditions were necessary.[18–20] Recently, the synthesis of biologically-active fused thiophenes employed a derivative of 2-aminothiophene 3-carboxylate in a low-yielding nucleophilic aromatic substitution.[21] Additionally, a Buchwald–Hartwig approach to N-arylation has been reported to proceed with an ethyl 2-aminothiophene-3-carboxylate derivative.[22] Although the use of commercially available aryl halides is advantageous, the need for expensive Pd catalyst systems, high reaction temperatures (100 °C), and inert conditions make an alternative approach to N-arylation of methyl 2-aminothiophene 3-carboxylate desirable.

Copper-mediated Chan–Lam coupling reactions[23,24] provide an important entry to heteroatom arylation and heteroarylation. The development of these cross-coupling reactions has attracted much attention because the reactions can typically be conducted at room temperature in open air in the presence of stoichiometric copper salt. Because of their robust nature, the Chan–Lam coupling has been utilized in N-arylation using a variety of amines, amino acid esters, anilines, imidazoles, and nitrogen heterocycles under these conditions.[25] Herein, a Chan–Lam cross-coupling protocol of methyl 2-aminothiophene-3-carboxylate (**1**) is revealed, providing broad access to this important chemical architecture. The results constitute an effective method for this N-arylation using mild conditions, starting from both arylboronic acids and aryltrifluoroborates. The use of aryltrifluoroborates, although unprecedented in this context, is especially attractive as these reagents are known to be easy to handle, bench-stable solids with favorable physical and chemical properties.[26–30]

Results and discussion

In initial screening, methyl 2-aminothiophene-3-carboxylate (**1**) was treated with phenylboronic acid (**2a**) or potassium

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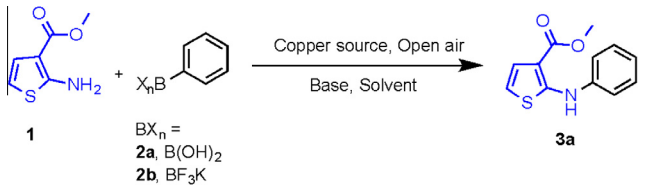


Scheme 1. Reaction of methyl 2-aminothiophene-3-carboxylate with phenylboronic acid and potassium phenyltrifluoroborate.

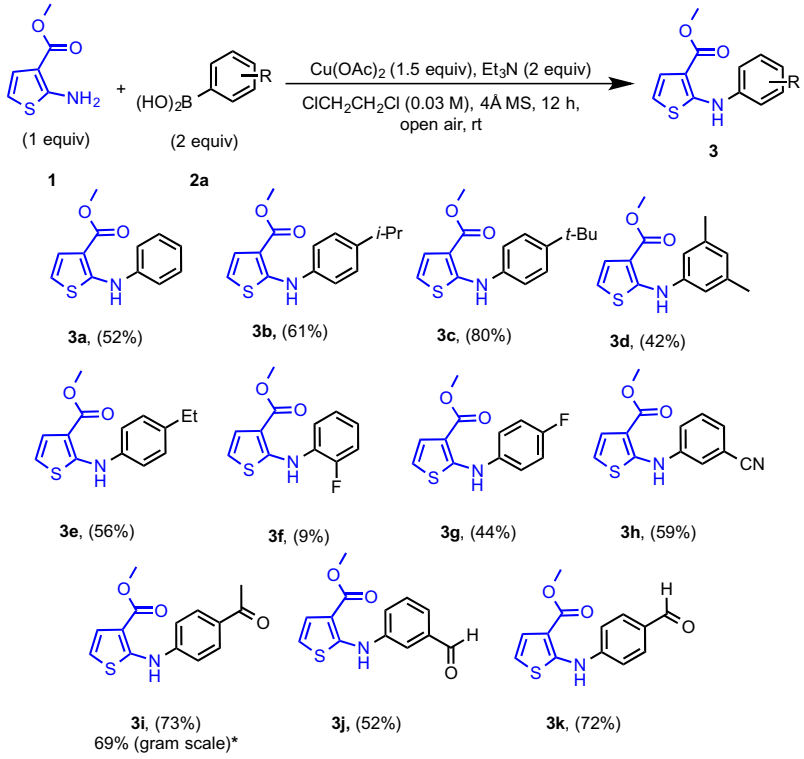
phenyltrifluoroborate (**2b**) (Scheme 1) in the presence of various copper sources, bases, and solvents in an open flask.

Comprehensive results and all screenings employed are shown in Tables S1–S3 (Supporting information). Various copper sources were screened, out of which $Cu(OAc)_2$ provided product **3a** with good conversion in the presence of Et_3N as base in $ClCH_2CH_2Cl$ at rt for 12 h. Unfortunately, attempts to drive these reactions to completion with longer reaction times (24 h) resulted in large quantities of diaryl substitution in preference to monoarylation. To minimize diaryl products, the reaction concentration was reduced to 0.03 M. Attempts to augment reactivity under either an oxygen or nitrogen atmosphere were made, however, open air was found to be most effective for obtaining good, reliable yields. With suitable conditions developed, various arylboronic acids were employed, and the scope of this coupling was evaluated (Table 1).

The reaction proved to be relatively insensitive to the electronic nature of the boron substrates. Arylboronic acids with electron-donating substituents (e.g., 4-isopropyl-, 4-*tert*-butyl-, and 4-ethylbenzeneboronic acids) afforded *N*-arylated products **3b**, **3c**, and **3e**, respectively, in modest to good yields. Substrates bearing electron-withdrawing moieties such as fluoro, cyano, formyl, and acetyl substituents also provided the desired products in good yields. In those instances where low yields were obtained (e.g., **3f**), starting material was typically recovered. To ensure the scalability and efficiency of this coupling, a gram-scale reaction generating **3i** was performed, and the desired product **3i** was obtained in good yield (69%).

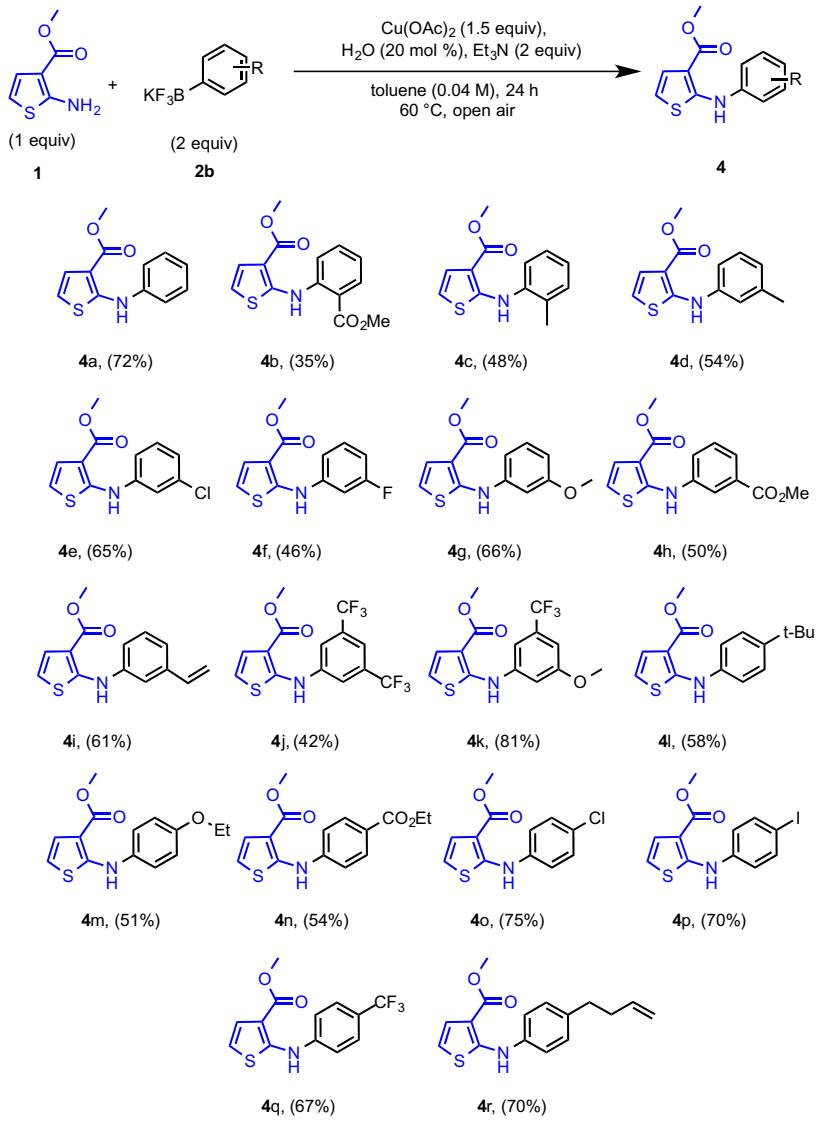
With the boronic acid scope demonstrated, the conditions developed for the coupling of 2-aminothiophene-3-carboxylate (**1**) were directly applied using potassium aryltrifluoroborates (**2b**). Unfortunately, these conditions resulted in only trace conversion. Fortunately, a slight modification of the reaction conditions identified a protocol for these substrates as well (Table S4: Supporting information). Using the original copper source and base, switching the solvent to toluene with a few drops of water at 60 °C in open air afforded the desired product in good yield. The role of water in aryltrifluoroborate cross-couplings has been well documented.[31–35] Thus, water is normally required to hydrolyze the trifluoroborates to boronic acids, the former thus serving as a stable reservoir for the more reactive boronic acid analogs. In this manner, bench stable aryltrifluoroborates were successfully cross-coupled with 2-aminothiophene-3-carboxylate (**1**) (Table 2). For the substrates incorporating electron-donating groups [2-methyl (**4c**), 3-methyl (**4d**), 4-*tert*-butyl (**4l**), 4-ethoxy (**4m**)], modest yields were obtained under optimized conditions. The 3-carboxymethyl derivative (**4h**) provided better yields as compared to the 2-carboxymethyl substrate (**4b**), perhaps owing to a decrease in steric hindrance. The substrates containing 3-vinyl (**4i**) and 4-carboxyethyl (**4n**) groups also the afforded desired products in good yields. Other electron-withdrawing groups were also well tolerated under the reaction conditions. For example,

Table 1
Substrate scope of N-arylation of methyl 2-aminothiophene-3-carboxylate with arylboronic acids



*Reaction performed on 1.0 g (6.36 mmol).

Table 2
Substrate scope of N-arylation of methyl 2-aminothiophene-3-carboxylate with aryltrifluoroborate



3-fluoro- (**4f**), 3,5-trifluoromethyl- (**4j**), 4-iodo- (**4p**), 4-trifluoromethyl-substituted aromatics (**4q**) were accessed in reasonable yields. 4-Trifluoroboratochlorobenzene provided **4o** in higher yield than the 3-chloro-substituted substrate produced **4e**. The 3-methoxy-5-trifluoromethyltrifluoroborate provided targeted product **4k** in excellent yield. Unfortunately, the optimized reaction conditions did not extend well to heteroaryltrifluoroborates or boronic acids.

In conclusion, a practical approach to the synthesis of *N*-arylated aminothiophene carboxylate analogs has been developed involving mild conditions. A variety of functional groups were well tolerated using stable, commercially available aryltrifluoroborates as well as arylboronic acids and inexpensive copper acetate. Efforts toward screening the biological activities of these newly synthesized compounds are ongoing.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.10.080.

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