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Synthesis of Bifunctional Thiophenes via Fiesselmann Condensation of Ynone Trifluoroborate Salts

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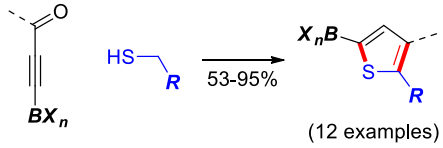
Supporting Information Placeholder



ABSTRACT: Ynone trifluoroborate salts undergo a base-promoted condensation reaction with alkylthiols to generate thiophene boronates with complete regiocontrol. The products are isolated in high yield and can be further derivatized through conventional C-B bond functionalization reactions.

The reaction of 2-mercapto acetate and ynones/ynoates (Fiesselmann synthesis) is a relatively under-exploited method for the generation of thiophene 2-carboxylate derivatives.[1] Nonetheless, there are many attractive features of this reaction, including the regiocontrolled assembly of a trisubstituted thiophene under mild reaction conditions. However, the potential of this process to deliver thiophenes bearing multiple orthogonal points of diversity has not yet been realized.

We have a long-standing interest in the synthesis of aromatic boronic acid derivatives via ring forming strategies.[2] Thus far, we have employed cycloadditions,[3] cyclizations[4] and electrocyclic reactions[5] towards this end. As shown in Figure 1, we anticipated that the utilization of borylated ynones in the Fiesselmann reaction would provide a direct and regiocontrolled means for accessing thiophenes bearing boronate and carboxylate ester groups. This approach would complement existing methods that rely on metal-halogen exchange for introduction of the boronate group, and would have the advantage of obviating any incompatibilities with the ester group. We report herein the successful realization of this concept by the use of ynone trifluoroborate salts,[6] and the scope of this reaction for thiol partners other than 2-mercapto acetates.

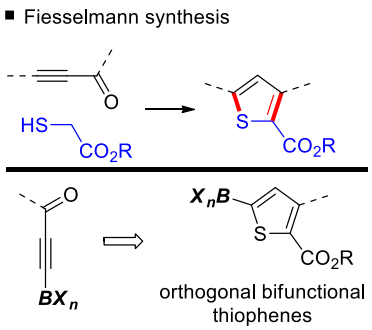
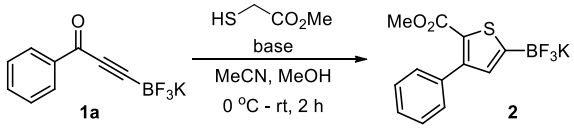


Figure 1. Proposed Fiesselmann synthesis of thiophene trifluoroborate salts.

We began our studies by exploring the reaction of methyl thioglycolate with ynone **1a** using various bases and dehydrating agents. The reaction was conducted as a one-pot process that involved addition of thiol to the ynone followed by base promoted condensation. The poor solubility of trifluoroborate salts limited the range of solvents that we could use, but pleasingly stirring the thiol and ynone salt in acetonitrile followed by addition of Cs_2CO_3 and $MgSO_4$ in MeOH generated the desired thiophene **2** after 2 h, albeit in low conversion (Table 1, entry 1). Increasing the amount of base was sufficient to promote full conversion of the ynone within 2 h, allowing the product to be isolated in good yield. We were concerned by the possibility of cation exchange in these reactions, potentially leading to mixtures of potassium and cesium salts that

Table 1. Optimization of the thiophene synthesis



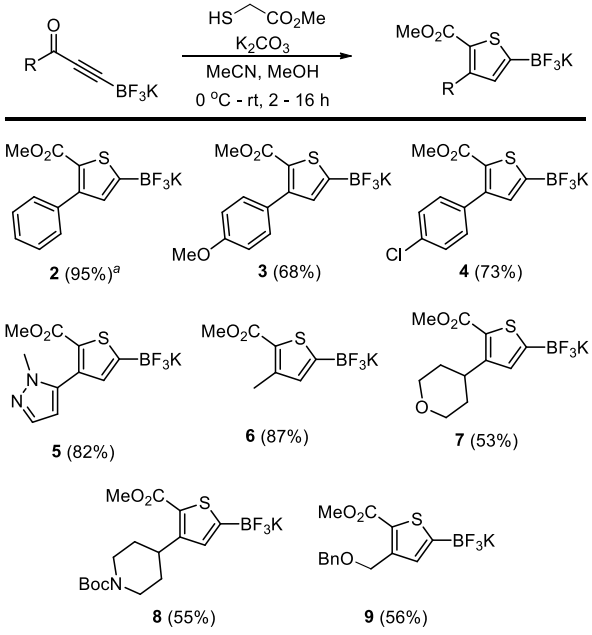
entry	thiol (equiv)	base (equiv)	additive	yield
1	1.0	Cs_2CO_3 (1)	$MgSO_4$	50%[a]
2	1.1	Cs_2CO_3 (2)	$MgSO_4$	50%
3	1.1	K_2CO_3 (2)	$MgSO_4$	40%
4	1.1	K_2CO_3 (2)	none	75%

[a] Conversion estimated by ^{19}F NMR spectroscopy.

would be difficult to discern and thereby leading to inaccurate yield measurements. This issue was circumvented by the use of K_2CO_3, and moreover, we found that the addition of $MgSO_4$ was not essential. Indeed, its removal from the reaction greatly facilitated purification leading to higher product yields. The successful condensation of thioglycolate and **1a** highlights the remarkable compatibility of trifluoroborate salts with the conditions required for heterocycle synthesis via condensation reactions.[7]

We next decided to explore the scope of the reaction with respect to the ynone substrate, and our results are summarized in Scheme 1. Both aromatic- and heteroaromatic-substituted ynones were well tolerated giving excellent isolated yields for the desired products. Alkyl substituted ynones also underwent the thiophene forming reaction, although these reactions were significantly slower and required overnight stirring to reach completion. Nonetheless, the examples depicted in Scheme 1 highlight the suitability of this method for rapidly constructing thiophenes with diverse orthogonal functionality.

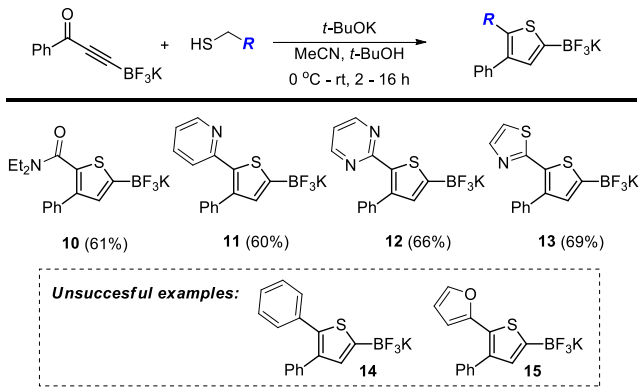
Scheme 1. Scope of ynones for thiophene synthesis



[a] Reaction carried out on 2.0 g of alkynyltrifluoroborate salt.

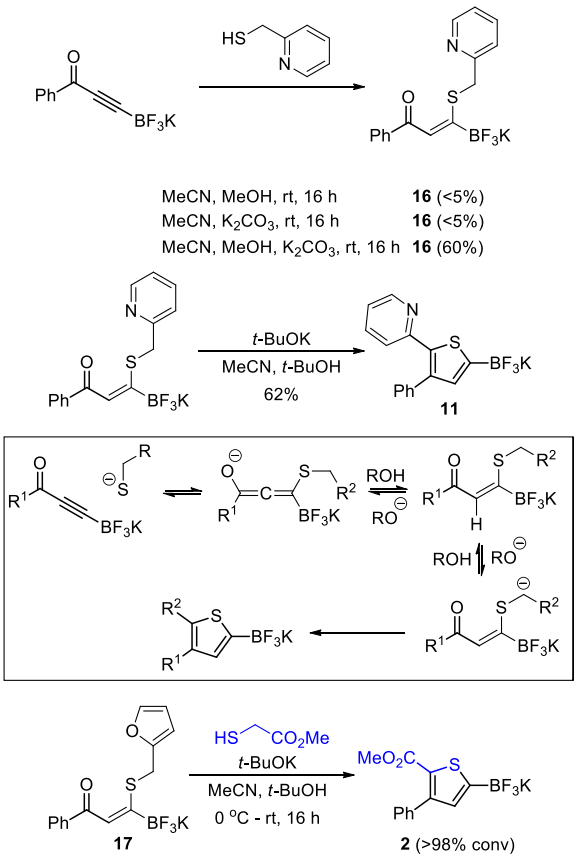
The Fiesselmann reaction has been almost exclusively restricted to the use of 2-mercapto acetates.[8] The potential of this method to be used on a wider range of thiols has not been established and so we took the opportunity to briefly explore the compatibility of other thiols with this process, our results are shown in Scheme 2. In the event, potassium carbonate was ineffective in this process but the use of t-BuOK/t-BuOH promoted the successful condensation of a thioglycolamide to give **10** in good yield. Moreover, the reaction was successfully extended to azinemethyl thiols to give **11** and **12**, as well as thiazole derivative **13**. Disappointingly however, more electron rich arylmethyl thiols were unsuccessful, and **14** and **15** were not accessible by this process.

Scheme 2. Scope of thiols for thiophene synthesis



In order to understand the limitations of the condensation reaction in more detail, we investigated the reaction of pyridine methylthiol in the presence/absence of base and protic solvent. Interestingly, we found that both K_2CO_3 and MeOH were required to promote addition to the ynone, and that stronger base was needed to mediate the final condensation step (Scheme 3). We therefore speculate that the addition of the thiol to the ynone proceeds reversibly, and that this intermediate can undergo proton transfer to generate an α-S anion that is further transformed to the thiophene. In cases where the α-thioether proton is not sufficiently acidic, allenoate formation predominates leading to an equilibrium mixture of ynone and β-thioethers. Finally, evidence for the reversibility of the first step was gathered by subjecting furan derived thioether **17** with methyl thioglycolate in the presence of t-BuOK/t-BuOH which cleanly generated the corresponding thiophene 2-carboxylate derivative **2**.

Scheme 3. Mechanistic studies

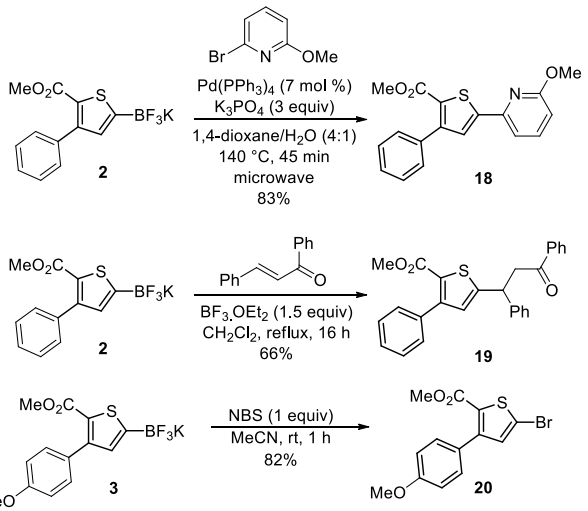


Our final objective was to explore the reactivity of the thiophene trifluoroborate salts in some representative C-B functionalization reactions. As shown in Scheme 4, compound **2**

underwent smooth cross coupling to give biaryl **18** in high yield. Moreover, we were able to carry out the 1,4-addition of **2** to an enone.[9] Finally, chemoselective bromodeborylation of **3** generated the corresponding bromide **20**, despite the potential for electrophilic aromatic substitution at various other sites.

In conclusion, we have developed a simple and regioselective method for the synthesis of thiophene trifluoroborate salts through a Fiesselmann condensation reaction. The reaction appears to be restricted to alkylthiols bearing electron deficient substituents, a property that we put down to partitioning of intermediates between allenoate and α-thioether anions; the former offers an elimination pathway while the latter can be product forming.

Scheme 4. Functionalization reactions



ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data. The Supporting Information is available free of charge on the ACS Publications website.

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