Decarboxylative trifluoromethylthiolation of pyridylacetates

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Abstract
Decarboxylative trifluoromethylthiolation of lithium pyridylacetates was achieved using N-(trifluoromethylthio)benzenesulfonylimide as the electrophilic trifluoromethylthiolation reagent. The reaction afforded the corresponding trifluoromethyl thioethers in good yield. Furthermore, the preparation of lithium pyridylacetates by saponification of the corresponding methyl esters and subsequent decarboxylative trifluoromethylthiolation were performed in a one-pot fashion.

Introduction
The pyridine ring is found in numerous biologically active compounds. Therefore, efficient methods for synthesizing substituted pyridines are in high demand in pharmaceutical and agricultural chemistry [1, 2]. Because of the unique features of fluorine atoms, fluorinated functional groups have also been recognized as important substructures in the design of medicinally relevant compounds [3-6]. Introducing a trifluoromethylthio group (CF₃S–), which has high lipophilicity and strong electron-withdrawing properties, into medicinal compounds can improve their pharmacokinetic properties [7-11]. Hence, the development of a synthetic method for the preparation of trifluoromethyl thioethers has recently attracted much attention [12-15].

Previously, our research group achieved decarboxylative functionalization of tertiary β-ketocarboxylic acids by exploiting their special ability to readily undergo decarboxylation [16-21]. During the course of this study, we found that lithium pyridylacetates undergo decarboxylative fluorination upon treatment with an electrophilic fluorination reagent to afford fluoromethylpyridines under catalyst-free conditions. Furthermore, we demonstrated the one-pot synthesis of fluoromethylpyridines from methyl pyridylacetates by saponification of methyl esters and subsequent decarboxylative fluorination (Scheme 1a) [21]. Herein, we describe the application of this method to decarboxylative trifluoromethylthiolation with an electrophilic trifluoromethylthiolation reagent (Scheme 1b) [22], which enables easy installation of the trifluoromethylthio group at a pyridyllic carbon.

Results and Discussion
First, we synthesized lithium 2-pyridylacetate 1a according to our previously reported procedure [21] and subjected it to decarboxylative trifluoromethylthiolation with N-trifluoro-
Scheme 1: Electrophilic decarboxylative functionalization of 2-pyridylacetates.

**Scheme 1**

![Scheme 1](image)

**Table 1:** Screening of reaction conditions.

| entry | [SCF₃⁺] | solvent | time (h) | yield of 2a (%) | yield of 3a (%) |
|-------|---------|---------|----------|-----------------|-----------------|
| 1     | 4       | DMF     | 15       | 0               | 0               |
| 2     | 5       | DMF     | 72       | 0               | 0               |
| 3     | 6       | DMF     | 3        | 14              | 31              |
| 4ᵃ    | 6       | DMF     | 5        | 30              | 34              |
| 5ᵃ    | 6       | DMSO    | 5        | 64              | 21              |
| 6ᵃ    | 6       | acetonitrile | 8       | 77              | 0               |
| 7ᵃ    | 6       | toluene | 168      | 72              | 0               |
| 8ᵃ    | 6       | CH₂Cl₂  | 72       | 54              | 0               |
| 9ᵃ    | 6       | t-BuOMe | 72       | 55              | 0               |
| 10ᵃ   | 6       | 1,4-dioxane | 9       | 75              | 0               |
| 11ᵃ   | 6       | THF     | 8        | 89              | 0               |
| 12    | 6       | THF     | 8        | 63              | 26              |
| 13ᵇ,a | 6       | THF     | 8        | 70              | 0               |

ᵃThe reaction was carried out with MS 4 Å (180 mg/0.2 mmol);ᵇ1.1 equiv of 6 was used.
2a was dramatically improved to 89% (Table 1, entry 11). In the absence of MS 4 Å, the yield of 2a was diminished even when the reaction was carried out in THF (Table 1, entry 12).

With the optimized reaction conditions in hand, we examined the one-pot synthesis of 2a from methyl ester 7a. Methyl 2-pyridylacetate 7a were saponified with lithium hydroxide in a MeOH/H2O system. After completion of the reaction, the solvents were evaporated under reduced pressure. Then, THF, MS 4 Å, and 6 were added to the residue, and the mixture was stirred at room temperature for 8 h. This reaction successfully afforded the desired product 2a in 85% yield over two steps (Scheme 2).

Encouraged by the aforementioned result, we applied this method to several 2-pyridylacetates (Scheme 3). Methyl 2-pyridylacetates 7b–d with arylmethyl substituents furnished the corresponding trifluoromethylthiolated products 2b–d in good yields. α,α-Dialkyl-2-pyridylacetates 7e–g also gave the desired products 2e–g in moderate yields. The method could also be applied to substrates with quinoline and isoquinoline backbones to afford the corresponding products 2h and 2i. In addition, the reaction of α-monosubstituted 2-pyridylacetate 8 was performed to yield the corresponding mono-trifluoromethylthiolated product 9 in 36% yield, along with 6% yield of disubstituted product 10 (Scheme 4). Increasing the amount of 6 did not improve the yield of products 9 and 10 significantly.

Based on the abovementioned results and our previous study on decarboxylative fluorination [21], we propose a plausible mechanism for this reaction, as outlined in Scheme 5. An electrophilic sulfur atom of 6 approaches the nitrogen atom on the pyridine ring to promote decarboxylation via the formation of N-trifluoromethylthio-2-alkylidene-1,2-dihydropyridine intermedi-
Scheme 4: Reaction of α-monosubstituted 2-pyridylacetates.

\[
\begin{array}{c}
\text{Ph} \\
\text{CO}_2\text{Me} \\
\text{N}
\end{array}
\rightarrow
\begin{array}{c}
\text{Ph} \\
\text{CO}_2\text{Li} \\
\text{N}
\end{array}
\xrightarrow[	ext{MeOH/H}_2\text{O (3:1)} \ 60^\circ\text{C}, 6\ h]{\text{LiOH (1.5 equiv)}}
\begin{array}{c}
\text{Ph} \\
\text{CO}_2\text{Li} \\
\text{N}
\end{array}
\rightarrow
\begin{array}{c}
\text{Ph} \\
\text{SCF}_3 \\
\text{N}
\end{array}
+ \begin{array}{c}
\text{Ph} \\
\text{SCF}_3 \\
\text{N}
\end{array}
\xrightarrow{\text{THF, rt. 25 h MS 4 Å}}
\begin{array}{c}
\text{Ph} \\
\text{SCF}_3 \\
\text{N}
\end{array}
\begin{array}{c}
\text{Ph} \\
\text{SCF}_3 \\
\text{N}
\end{array}
\begin{array}{c}
\text{9} \\
\text{10}
\end{array}
\]

| 6 | yield of 9 | yield of 10 |
|---|------------|-------------|
| 1.1 equiv | 36% | 6% |
| 5.0 equiv | 34% | 11% |

Scheme 5: Proposed reaction pathway.

\[
\begin{array}{c}
\text{N}
\end{array}
\xrightarrow{\text{6}}
\begin{array}{c}
\text{Ph} \\
\text{S-CF}_3 \\
\text{N}
\end{array}
\xrightarrow{\text{Ph}}
\begin{array}{c}
\text{Ph} \\
\text{S-CF}_3 \\
\text{N}
\end{array}
\xrightarrow{\text{Li}^+}
\begin{array}{c}
\text{Ph} \\
\text{S-CF}_3 \\
\text{N}
\end{array}
\]

\[
\begin{array}{c}
\text{N}
\end{array}
\xrightarrow{\text{6}}
\begin{array}{c}
\text{R}^1 \text{R}^2 \\
\text{SCF}_3 \\
\text{N}
\end{array}
\]

\[
\begin{array}{c}
\text{Ph} \\
\text{S-CF}_3 \\
\text{N}
\end{array}
\xrightarrow{\text{Ph}}
\begin{array}{c}
\text{Ph} \\
\text{S-CF}_3 \\
\text{N}
\end{array}
\xrightarrow{\text{Li}^+}
\begin{array}{c}
\text{Ph} \\
\text{S-CF}_3 \\
\text{N}
\end{array}
\]

Methyl 4-pyridylacetate 11 also gave the corresponding trifluoromethylthiolated product 12 in 29% yield (Scheme 6), where the reaction was assumed to proceed via the N-trifluoromethylthio-4-alkylidene-1,4-dihydropyridine intermediate. In contrast, methyl 3-pyridylacetate 13 did not yield the trifluoromethylthiolated product at all, despite complete saponification of the methyl ester.

Conclusion

In conclusion, we demonstrated the decarboxylative trifluoromethylthiolation of lithium 2- and 4-pyridylacetates to synthesize pyridine derivatives with a trifluoromethylthio group at a tertiary carbon center adjacent to the pyridine ring. Furthermore, saponification of methyl pyridylacetates and subsequent decarboxylative trifluoromethylthiolation of the resulting lithium salts were performed in a one-pot fashion. This method can
easily convert an ester group into a trifluoromethylthio group. The resulting trifluoromethylthio ethers would be useful for the preparation of various medicinally relevant compounds.

Supporting Information
Experimental procedures, characterization data, and copies of NMR spectra.

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