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## Graphical Abstract

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**Phosphine-Mediated Synthesis of Trifluoromethyl Substituted Pyrroles Using TFAA as the $CF_3$ Source**

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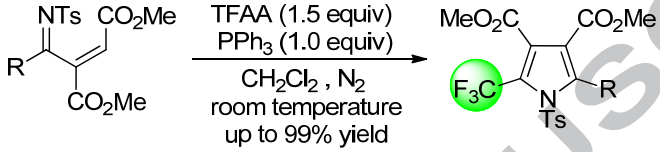

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# Phosphine-Mediated Synthesis of Trifluoromethyl Substituted Pyrroles Using TFAA as the $CF_3$ Source

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ABSTRACT

A phosphine-mediated synthesis of trifluoromethyl substituted pyrrole derivatives was achieved. The method described here is very fast, operationally simple and easily amenable to scale-up, and commercially available trifluoroacetic anhydride (TFAA) is used as the only trifluoromethyl source. A wide range of products were obtained with good yields under mild condition using this method.



The incorporation of trifluoromethyl group often leads to significant changes in the physical and chemical properties of molecules such as solubility, metabolic stability, and bioavailability, etc.[1] Organic compounds bearing trifluoromethyl group have so far been widely applied in the fields of functional materials, agrochemicals and pharmaceutical due to their special properties.[2] Therefore, the development of new methodologies for the synthesis of trifluoromethyl-substituted compounds is undoubtedly one of the most exciting and dynamic areas in contemporary organic synthesis, especially the development of reliable and powerful methods using simple and readily available trifluoromethyl sources.[3] Among these useful compounds, trifluoromethyl-substituted pyrrole is an important subclass due to the prevalence of such motif in pharmaceutical compounds and natural products.[4-5] These bioactive compounds have been shown to exhibit significant insecticidal and medical activities, such as the insecticide Chlorfenapyr,[6] general anesthesia inducer,[7] antitumor compound,[8] and numerous others (Figure 1). Although a few elegant approaches have been developed for the construction of trifluoromethyl-substituted pyrroles,[9] the synthesis of such compounds is still a significantly challenging task due to some major problems such as the use of costly transition metals, high time-consumption, high temperature and low efficiency.[10] Therefore, the development of an efficient method is highly desired. Our group has been focusing on the development of various trifluoromethylation methods for some time,[11] and has reported a highly efficient method for the synthesis trifluoromethylated furans.[12] We found that other than many reported special-tailored trifluoromethyl sources, trifluoroacetic anhydride (TFAA), one of the most common reagents, can be used as a powerful $CF_3$ transfer reagent. Encouraged by this promising finding, we envisioned that

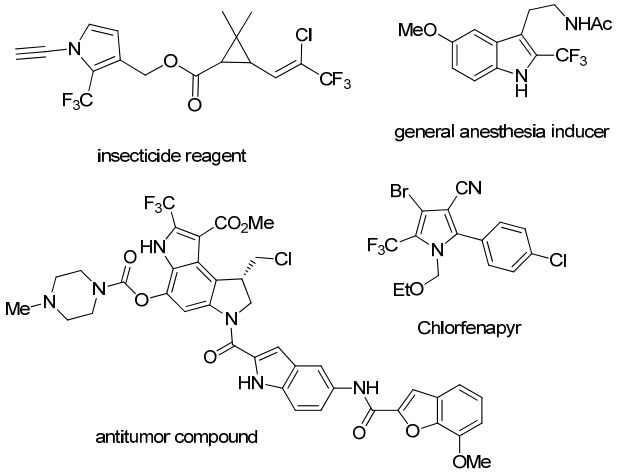


**Figure 1**. Examples of biologically important pyrrole derivatives

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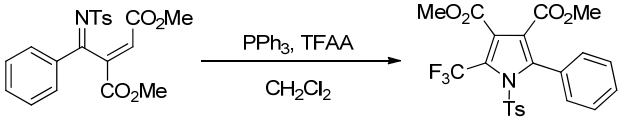
trifluoromethylated pyrroles might be efficiently synthesized by employing TFAA as well.

**Table 1**. Screening for Optimal Conditions for the Trifluoromethylated Pyrrole[a]




**1a** **2a**

| Entry | Solvent | TFAA (equiv) | $PPh_3$ (equiv) | Yield (%)[b] |
|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | 1.3 | 1.0 | 93 |
| 2 | $CH_2Cl_2$ | 1.3 | 1.5 | 91 |
| 3 | $CH_2Cl_2$ | 1.5 | 0.5 | 48 |
| 4 | $CH_2Cl_2$ | 1.5 | 1.0 | 99 |
| 5 | $CH_2Cl_2$ | 1.5 | 1.5 | 94 |
| 6 | toluene | 1.5 | 1.0 | 97 |
| 7 | $CH_3CN$ | 1.5 | 1.0 | 96 |
| 8 | THF | 1.5 | 1.0 | 89 |
| 9 | xylene | 1.5 | 1.0 | 91 |
| 10 | MeOH | 1.5 | 1.0 | 23 |

[a] Unless otherwise noted, the reaction was performed with **1a** (0.20 mmol), TFAA (0.30 mmol), and $PPh_3$ (0.20 mmol) in solvent (1.0 mL) at room temperature within 1 min. [b] Yield of isolated product. equiv = equivalent.

Compound **1a** with TFAA in the presence of $PPh_3$ were chosen for initial optimization of the reaction parameters at room temperature (Table 1, entry 1). Indeed, the desired reaction was found to take place and afforded the product in 93% yield. Further optimizing conditions by adjusting the amount of $PPh_3$ and TFAA revealed that the result of the 99% yield (Table 1, entry 4) was achieved using 1.0 equiv of $PPh_3$ and 1.5 equiv of TFAA. Results of experiments in various solvents (Table 1, entries 6–10) showed that the reaction has a wide adaptability for different solvents except for MeOH, the yield with which is merely 23%. The structure of the product was unequivocally established by the X-ray crystallography of **2h**.[13]

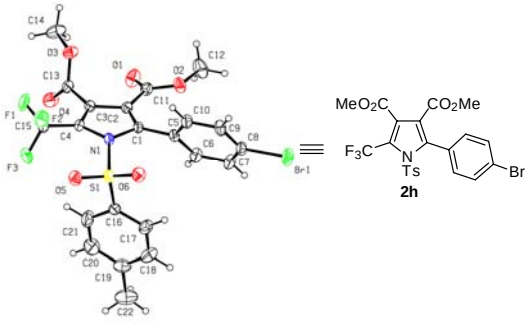
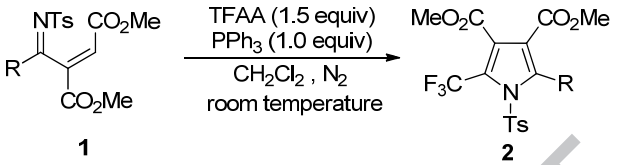



**Figure 2**: The X-ray structure of compound **2h**.

To further investigate the scope and limitation of this reaction, various types of substrates were tested in the cascade process under the optimal reaction condition (Table 2). Results show that almost all the substrates were well tolerated with satisfying yields (Table 2, 65%–99%), including both of the electron-withdrawing and -donating groups substituted substrates. However, the yields with the heterocyclic substituted substrates were not as high as expected, i.e. 65% to 68% as listed in entry 14 and 15 of Table 2. As also can be seen from the results, the substitution positions have no obvious influence on the reaction behavior (Table 2, entries 6–7, 9–11).

**Table 2**. Substrate Scope[a]

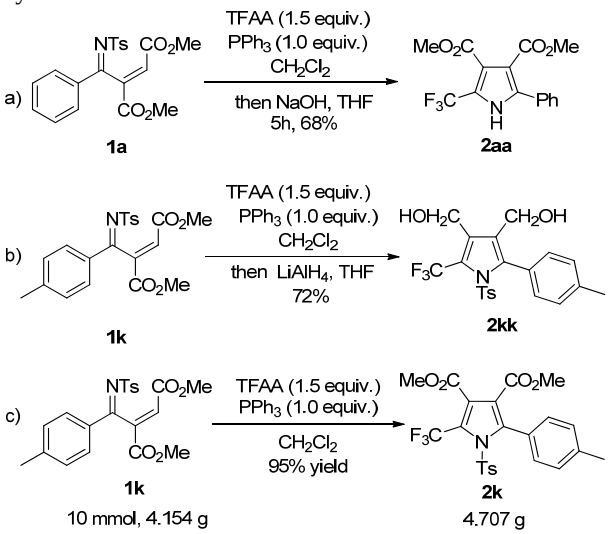



**1** **2**

| Entry | **1** | R | Products | Yield (%)[b] |
|---|---|---|---|---|
| 1 | **1a** | Ph | **2a** | 99 |
| 2 | **1b** | 2-Naphthyl | **2b** | 87 |
| 3 | **1c** | 3-$NO_2C_6H_4$ | **2c** | 95 |
| 4 | **1d** | 4-$CF_3C_6H_4$ | **2d** | 94 |
| 5 | **1e** | 2-$FC_6H_4$ | **2e** | 97 |
| 6 | **1f** | 3-$ClC_6H_4$ | **2f** | 95 |
| 7 | **1g** | 4-$ClC_6H_4$ | **2g** | 96 |
| 8 | **1h** | 4-$BrC_6H_4$ | **2h** | 90 |
| 9 | **1i** | 2-$MeC_6H_4$ | **2i** | 90 |
| 10 | **1j** | 3-$MeC_6H_4$ | **2j** | 97 |
| 11 | **1k** | 4-$MeC_6H_4$ | **2k** | 95 |
| 12 | **1l** | 4-$OMeC_6H_4$ | **2l** | 91 |
| 13 | **1m** | 3,4-$(OCH_2O)C_6H_3$ | **2m** | 92 |
| 14 | **1n** | 2-furyl | **2n** | 68 |
| 15 | **1o** | 2-thienyl | **2o** | 65 |

[a] Unless otherwise noted, the reaction was performed with **1** (0.2 mmol), TFAA (0.3 mmol), and $PPh_3$ (0.2 mmol) in $CH_2Cl_2$ (1.0 mL) at room temperature within 1 min. [b] Yield of isolated product.

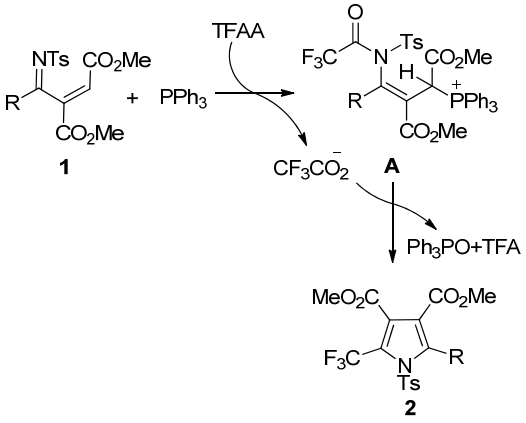
**Scheme 1.** One-pot Synthesis of **2aa** and **2kk** and Scalable Synthesis of **2k**




To further investigate the synthetic value of the products from the present transformation, one-pot removal of Ts group of the product was conducted. It was found that the Ts group could be smoothly removed with treatment of **2a** with NaOH in the same vessel in THF, delivering N-free trifluoromethylated pyrrole **2aa** in 68% yield from **1a** (Scheme 1a). Furthermore, a one-pot sequential pyrrole formation/reduction was also successful in affording the desired products with good yield (**2kk**, 72%) (Scheme 1b). Additionally, when the present reaction was

performed on a 10 mmol scale (**1k**, 4.154 g), the reaction remained fast and efficient with 95% yield (Scheme 1c). Thus we can conclude that the reaction proposed in this paper is fast, efficient and adaptable to gram-scale synthesis.

**Scheme 2**. Possible Reaction Pathways




On the basis of our experimental results, a plausible approach is outlined in scheme 2. Nucleophilic addition of Lewis basic $PPh_3$ to **1** generates a highly reactive zwitterionic intermediate **A** in the presence of TFAA, which then undergoes the intramolecular Wittig reaction on the assistance of conjugate base of TFA, affording the corresponding trifluoromethylated pyrrole **2**.

In conclusion, we have developed a phosphine-mediated cascade transformation for the synthesis of trifluoromethyl pyrroles using readily available trifluoroacetic anhydride as a $CF_3$ source. The reaction is operationally simple with wide substrate generality and amenable to scale-up, furnishing trifluoromethyl substituted pyrroles in high yields under mild conditions.

## Acknowledgments

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## Supplementary data

Supplementary data (compound characterization data) associated with this article can be found, in the online version, at

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13. Crystallographic data for compound **2h** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-972951. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.Uk).