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One-pot synthesis of α-trifluoromethylstyrenes from aryl ketones and the Ruppert–Prakash reagent

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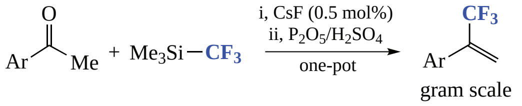
A new synthesis of α-trifluoromethylstyrenes from aromatic ketones and (trifluoromethyl)trimethylsilane is described. The reaction involves nucleophilic trifluoromethylation and elimination of trimethylsilanol, which are performed within one reaction flask.



Keywords: organofluorine compounds, trifluoromethylation, silicon reagents, ketones, alkenes.

Importance of organofluorine compounds in medicinal chemistry and agrochemistry[1] has stimulated the development of methods for their synthesis. α-Trifluoromethylstyrenes **1** have emerged as valuable building blocks for the synthesis of compounds bearing either trifluoromethyl group or difluoromethylene fragment.[2] Indeed, the double bond of these styrenes may be attacked by nucleophiles[3] and radicals[4] or involved into transition metal catalyzed[5] and cycloaddition reactions.[6]

Styrenes **1** can be constructed by copper[7] or palladium (or nickel)[8] catalyzed cross-couplings or by carbonyl olefination reactions[9] (Figure 1). However, these processes utilize expensive catalysts and require synthesis of starting compounds. An alternative approach is based on elimination of water from the CF_3-substituted alcohols, but this step proceeds under very harsh conditions[10] or requires an additional step of derivatization of the hydroxyl into a good leaving group.[11]

Herein we report a practical one-pot synthesis of styrenes **1** from aromatic ketones and (trifluoromethyl)trymethylsilane **2**. This silane known as the Ruppert–Prakash reagent is the most widely used reagent for the direct introduction of the trifluoromethyl group.[12] It is an air stable liquid and is commercially available even on a kilogram scale. In the presence of Lewis basic activators, this silane generates a five-coordinate siliconate species[13] serving as a source of the trifluoromethyl carbanion[14] which would attack the keto group.[15] We report that under acidic conditions, the intermediate silyl ethers can undergo elimination of the trimethylsilanol thereby allowing for a convenient one step protocol for the synthesis of styrenes **1**.

We performed the reactions starting from 5 g of ketones, which provides access to gram quantities of the styrenes. First, ketones were treated with 1.1 equiv. of the Ruppert–Prakash reagent in the presence of as little as 0.5 mol% of cesium fluoride (Scheme 1). As a solvent, small amount of THF was used, 10 ml per 5 g of the ketone. The silane had to be slowly added to a mixture of the ketone and cesium fluoride to maintain the temperature below 20 °C, since at higher temperatures formation of the silyl enol ethers could take place, which is accompanied by the evolution of gaseous trifluoromethane. From the resulting mixture, THF was evaporated under vacuum, and the residue was treated with 0.5 equiv. of phosphorus pentoxide and small amount of concentrated sulfuric acid, and the mixture was heated at 100 °C for short period of time (from 15 min to 1 h). For volatile styrenes, the mixture was directly subjected to distillation at atmospheric pressure or under mild vacuum, while for others, the mixture was first extracted, the extracts were washed to remove acidic impurities, and then purified by vacuum distillation. Of special note is that the products were not contaminated with hexamethyldisiloxane (TMS_2O), since the trimethylsilyl fragment remains bound in the form of non-volatile silyl derivatives of polyphosphoric and sulfuric acids. The elimination proceeds faster with substrates bearing electron donating substituent suggesting that E1 mechanism is likely.

The method was applied to methyl, methoxy and halogen-substituted ketones, as well as to α- and β-acetonaphthones. For

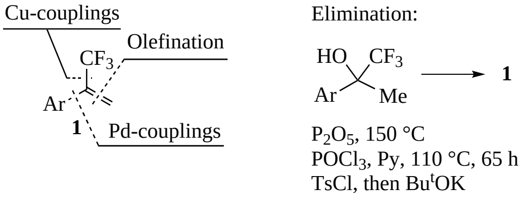
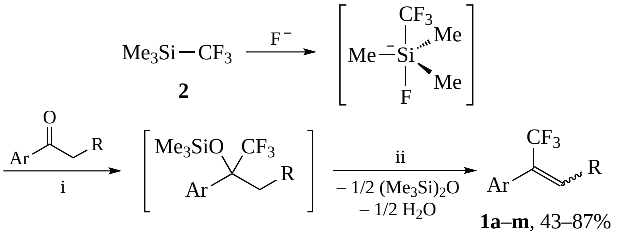


Figure 1 Approaches for the synthesis of styrenes **1**.



a Ar = Ph, R = H
b Ar = 4-MeC_6H_4, R = H
c Ar = 1-naphthyl, R = H
d Ar = 2-naphthyl, R = H
e Ar = 4-$MeOC_6H_4$, R = H
f Ar = 3-$MeOC_6H_4$, R = H
g Ar = 2-$MeOC_6H_4$, R = H
h Ar = 4-FC_6H_4, R = H
i Ar = 4-ClC_6H_4, R = H
j Ar = 4-BrC_6H_4, R = H
k Ar = 4-PhC_6H_4, R = H
l Ar = 2-thienyl, R = H
m Ar = Ph, R = Me (*E*/*Z* = 1 : 1)

Scheme 1 *Reagents and conditions*: i, aryl ketone (5 g, 25–42 mmol, 1 equiv.), Me_3SiCF_3 (1.1 equiv.), CsF (0.5 mol%), THF, 0–20 °C, 1 h; ii, P_2O_5 (0.5 equiv.), H_2SO_4 (0.25 equiv.), or MsOH (0.25 equiv.) for **1l**, 100 °C, 15–60 min.

the most electron rich substrate bearing the thiophene system, methanesulfonic acid was used to avoid aromatic sulfonation leading to the expected product **1l** in 54% yield. The reaction of propiophenone afforded alkene **1m** in reasonable yield as a mixture of *E*/*Z* isomers.

In summary, a convenient protocol for the synthesis of α-trifluoromethylstyrenes from aromatic ketones and a readily available silicon reagent is described. The reaction is conveniently performed within one laboratory step furnishing valuable products on a gram scale.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.09.030.

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