Direct Preparation of Trifluoromethyl Ketones from Carboxylic Esters: Trifluoromethylation with (Trifluoromethyl)trimethylsilane**

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Trifluoromethyl ketones are potential inhibitors of hydrolytic enzymes because of their ability to form stable hydrates, thereby acting as transition-state analogues of substrates for such enzymes.[1] The trifluoroacetyl group is also a highly electron-withdrawing substituent. Methods for the synthesis of trifluoromethyl ketones are scarce.[2] While trifluoromethyl aryl ketones can be obtained by Friedel–Crafts acylations,[3] alicyclic and aliphatic trifluoromethyl ketones are usually available only by multistep synthetic operations.[4, 5] This restricts their use and makes it difficult to handle complicated intermediates for pharmacologically interesting targets.

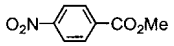
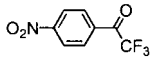
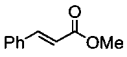
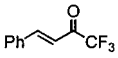
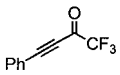
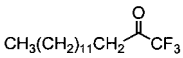
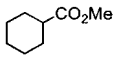
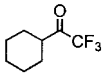
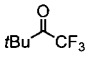
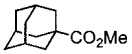
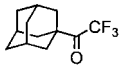
Trifluoromethyltrimethylsilane ($TMS\text{-}CF_3$, **2**) reacts with aldehydes and ketones under fluoride-induced trifluoromethyl transfer to yield trifluoromethyl alcohols.[6–8] The chemistry of $TMS\text{-}CF_3$ and related reagents was recently reviewed.[9] When α-keto esters are used as substrates in THF, $TMS\text{-}CF_3$ adds only to the keto group to give derivatives of Mosher's acid.[10] Simple unactivated esters are unreactive toward $TMS\text{-}CF_3$[11] in THF.

We now report on the first successful nucleophilic trifluoromethylation of esters with $TMS\text{-}CF_3$. This provides a straightforward and powerful synthetic tool to convert the ester functionality into the trifluoromethylcarbonyl group in one step without formation of double-addition products. A remarkable feature of this novel method is that it can be applied to non-enolizable as well as enolizable esters.

Reaction of methyl benzoate (**1a**) with $TMS\text{-}CF_3$ (1.25 equiv) in dry toluene smoothly gave 1,1,1-trifluoroacetophenone (**6a**) in 95% yield. The initiator, anhydrous tetrabutylammonium fluoride (TBAF; 2.5 mol% in THF) was added at $-78\,^{\circ}C$, and the reaction mixture was then allowed to warm slowly to room temperature, stirred for 18 h, and finally treated with 2 M hydrochloric acid. Addition of the initiator at $0\,^{\circ}C$ gave rise to mixtures of the corresponding trifluoromethyl ketone **6a** and bis-trifluoromethylated alcohol as a result of double addition.

Table 1 shows the optimized reaction conditions for each case. The yields are good to excellent. In anhydrous pentane as solvent, methyl myristate (**1e**) gave the corresponding trifluoromethyl ketone (**6e**) in 75% yield. α,β-Unsaturated methyl cinnamate (**1c**) gave exclusively the 1,2-addition product **6c** in 85% yield. Even sterically hindered esters, including methyl pivalate (**1g**) and methyladamantane 1-carboxylate (**1h**), reacted smoothly. However, in the case of methyl 3-phenylpropinate (**1d**), the desired product **6d** could not be isolated owing to extensive polymerization under the reaction conditions. In general, it is possible to use any nonpolar aprotic solvent, such as pentane, benzene, toluene, or dichloromethane. Although THF can also be used for some reactive esters such as **1a**, it is not the solvent of choice; THF undergoes slow ring opening by $TMS\text{-}CF_3$ under these conditions to yield detectable amounts of 5,5,5-trifluoro-1-trimethylsiloxypentane as a by-product. For the synthesis of low-boiling trifluoromethyl ketones, pentane is a good reaction medium, which nevertheless can be substituted by dichloromethane whenever solubility problems arise. The prerequisite for a successful reaction between esters and $TMS\text{-}CF_3$ is careful drying of all solvents and reagents. Therefore, a commercial solution of TBAF (1 M in THF) was dried for 4 h under a dry argon atmosphere over activated 4-Å molecular sieves (4 mL of solution per 1 g of molecular sieves) prior to use.

Table 1. Conditions and yields for reactions of $TMS\text{-}CF_3$ (1.25 equiv) with various esters induced by 2.5 mol% TBAF in THF.

	Reagent **1**	Solvent	t [h]	Product **6**	Yield [%]
a	$PhCO_2Me$	toluene	18		95
b		CH_2Cl_2	18		81
c		pentane	24		85
d		pentane	24		0[a]
e	$CH_3(CH_2)_{12}CO_2Me$	pentane	24		75
f		pentane	48		72
g	$tBu\text{-}CO_2Me$	pentane	72		68
h		pentane	72		70

[a] Extensive polymerization.

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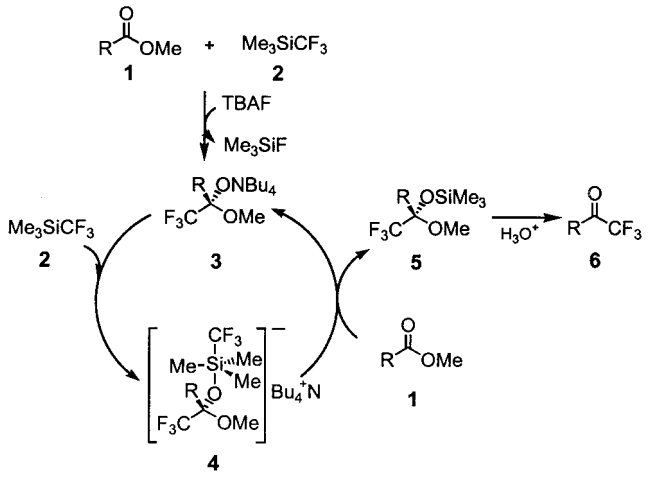
The mechanism for TMS-CF_3 addition is shown in Scheme 1. In the initiation step of the nucleophilic trifluoromethylation, TBAF reacts with TMS-CF_3 to transfer a CF_3 group to the ester. This gives rise to the deprotonated hemiacetal **3**, the true catalytic species. The latter in turn



Scheme 1. Proposed mechanism for the fluoride-induced nucleophilic trifluoromethylation of carboxylic esters with TMS-CF_3.

activates a second molecule of TMS-CF_3 through formation of a negatively charged pentacoordinated silicon species **4**, which transfers a CF_3 group to another ester molecule, resulting in formation of **5** and simultaneous regeneration of the catalytic species **3**.

However, when the initiator is added at higher temperatures (at or above 0 °C), **3** may decompose to give a methoxide ion, and the intermediate trifluoromethyl ketone, because of its high reactivity, may be subject to a second addition reaction.

In summary, we have developed a versatile method for the simple and efficient preparation of trifluoromethyl ketones from methyl esters.

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In Situ X-Ray Diffraction Study of the Initial Stages of Formation of MCM-41 in a Tubular Reactor**

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The successful preparation of MCM-41, a mesoporous silicate with hexagonally ordered cylindrical pores, has stimulated interest in this new class of composite materials since the pore sizes can be varied between 2 and 10 nm.[1, 2] Surfactants are used to induce the desired structure of the silicate polymer network. Usually, the synthesis of MCM-41 is carried out at surfactant concentrations at which the surfactant alone would not form a mesophase, which indicates a strong cooperative surfactant – silicate interaction. We describe here for the first time a continuous preparation of MCM-41 in a tubular reactor, which allows in situ X-ray diffraction (XRD) studies of the kinetics of mesophase formation on a mesoscopic length scale. The hexagonal mesophase is shown to form within the first three minutes of the reaction without passing through any intermediate phase. Different models have been developed to describe the formation of MCM-41. Beck et al.[2] proposed several possible pathways for the formation of such materials, and a more detailed, mechanistic model was presented by Monnier et al.[3] to account for the observation of an intermediate layered phase prior to reaching the hexagonal phase. This model introduced multidentate binding of silicate oligomers, preferred polymerization of silicate at the surfactant – silicate interface, and charge density matching as key factors in the formation of a surfactant – silicate mesophase. However, owing to the large number of different synthesis routes reported, each varying with respect to the silica source, surfactant concentration, pH, and the acid/base used etc., some of the reaction steps involved in the formation of the mesophase may differ depending on the applied experimental conditions. This is particularly important when organic precursors, such as tetraethoxysilane (TEOS), are used as the silica source, since their solubilities in aqueous solution are limited and therefore formation of an oil-in-water emulsion is expected as the initial reaction step. We describe here the results obtained by time-resolved in situ XRD measurements on the kinetics of formation of the hexagonal composite mesophase of such a system.

The reaction is too fast to allow data accumulation times long enough to obtain accurate kinetic data with a traditional setup for the investigation of liquids. To circumvent this problem, a tubular reactor was constructed and connected to a cell especially designed for XRD measurements of liquids; this allowed data accumulation times long enough to obtain a

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