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Nucleophilic Trifluoromethylation of Imines under Acidic Conditions

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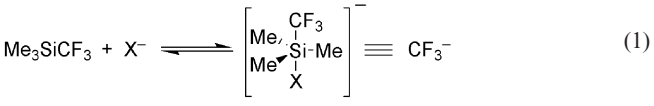
A general method for the trifluoromethylation of imines by using Me_3SiCF_3 under acidic conditions is described. The reaction is promoted by hydrofluoric acid generated in situ from KHF_2 and either TFA or TfOH. A new chemoselectivity pattern was achieved, as the C=N bond was found to be more reactivate than the carbonyl group. The trifluoromethylation reaction is believed to proceed by concerted transfer of the CF_3 group from the silicon atom to the iminium electrophile. (© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2008)

Introduction

As a result of the importance of compounds bearing a trifluoromethyl group for the pharmaceutical and agrochemical industries,[1] the development of trifluoromethylation reactions has been a subject of intense investigation.[2] Among different approaches for the introduction of a CF_3 group into organic molecules, the methodology of nucleophilic trifluoromethylation by using the Ruppert–Prakash reagent (Me_3SiCF_3)[3] has gained particular attention in recent years.[4–6]

Indeed, Me_3SiCF_3 is an available, shelf-stable, and easy-to-handle compound, and its nucleophilic reactivity is uncovered by Lewis basic activators, such as fluoride ions. The Lewis base mediated reactions of Me_3SiCF_3 proceed through the generation of five-coordinate species, which serve as CF_3 carbanion equivalent [Equation (1)].



(1)

Despite the fact that five-coordinate intermediates with a CF_3 group at the silicon atom have been identified,[7] the mechanism of their reaction with electrophiles has not been studied. Usually, it is implied that a free CF_3 carbanion is formed in this process. In accord with this notion is the considerable basicity of the Me_3SiCF_3/Lewis base system, which readily abstracts acidic protons to provide trifluoromethane,[8] thereby limiting the scope of this methodology.

Herein we report the first example of nucleophilic trifluoromethylation proceeding in the presence of strong protic acids. A switch from basic to acidic conditions leads to a new selectivity profile with the benefits of substrate scope and functional group compatibility issues.

In contrast to the well-elaborated trifluoromethylation of carbonyl compounds,[3b,4,5a,5b] reactions of the C=N bond with Me_3SiCF_3 are limited. Thus, only biased substrates such as nitrones,[9] azomethines activated by chelating Lewis acids,[10] and iminium ions[11] undergo smooth trifluoromethylation. Concerning neutral imines, their reactivity strongly depends on the substituent at the nitrogen atom. Substrates bearing an electron-withdrawing substituent react easily,[5b,12] whereas imines with an aryl group react under the more drastic conditions of naked fluoride ion activation.[13] At the same time, substrates possessing an alkyl or benzyl group at the nitrogen atom, which cannot stabilize the incipient negative charge, are unreactive, and their reactions with Me_3SiCF_3, as well as those with other trifluoromethylating reagents, have not been described.

Within the framework of our studies on trifluoromethylation[10,11a,11b] and pentafluorophenylation[14] of C=N bonds with the use of silicon reagents we demonstrated that *N*,*N*-dialkyliminium ions readily react with Me_3SiCF_3 in the presence of potassium fluoride if DMF is used as the solvent.[11a] This prompted us to test the behavior of iminium ions generated by protonation of imines under similar conditions.

Results and Discussion

It was rewarding to find that when a solution of imine **1a** in DMF was successively treated with an excess amount of trifluoroacetic acid (TFA), Me_3SiCF_3, and KF at 23 °C product **2a** was obtained in 86% yield [Equation (2)]. Because TFA and KF are expected to afford a solution of hy-

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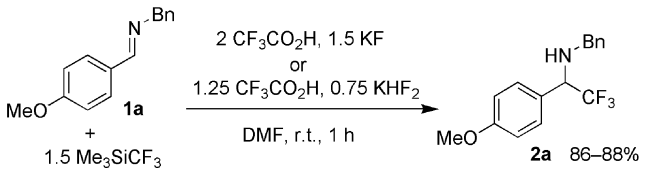
drofluoric acid, the use of KHF_2 in the presence of a reduced amount of acid was tested and shown to provide identical results. Consequently, KHF_2 was used for further studies.



(2)

It is worthy to note that these trifluoromethylation reactions occur under acidic conditions defined by an excess amount of TFA. To get a better understanding of this process, a brief screen of reaction parameters was undertaken. Interesting results were obtained on changing the order of mixing: the combination of KHF_2 and TFA in DMF gave a clear solution. Subsequent treatment of this solution with Me_3SiCF_3, stirring for 30 min at 0 °C, and addition of imine **1a** led to recovered imine, indicating that the silane was destroyed by the hydrofluoric acid. However, when the same experiment was performed in acetonitrile product **2a** was obtained in 90% yield. *The latter observation suggests that Me_3SiCF_3 and HF are compatible in acetonitrile.* A more decisive piece of evidence supporting this conclusion was provided by NMR spectroscopy. Thus, by mixing KHF_2, TFA (1.7 equiv.), and Me_3SiCF_3 (2 equiv.) in CD_3CN and by monitoring the resulting homogeneous solution by ^1H and ^{19}F NMR spectroscopy it was found that almost no decomposition of the silane occurred within 1 h at room temperature and only after 3 d was half of the silane converted into Me_3SiF.

Imine **1b** containing a nitro group instead of a methoxy group turned out to be much less reactive, and no product was formed in DMF. Therefore, for this substrate we decided to optimize the reaction conditions (Table 1). When the reaction was performed in MeCN, product **2b** was furnished in 71% yield after stirring for 15 h at room temperature (Table 1, Entry 3). On the basis of the assumption that the protonated imine serves as the electrophilic species in this process, we proposed that its reactivity could be increased by using a stronger acid. After considerable experimentation it was determined that employment of triflic acid in acetonitrile containing DMF (3 equiv.) afforded amine **2b** in 83% isolated yield (Table 1, Entry 7). In this case, DMF exhibits an accelerating effect on the trifluoromethylation, although decomposition of the silane is accelerated as well, and as a result, three equivalents of Me_3SiCF_3 should be used for complete conversion.

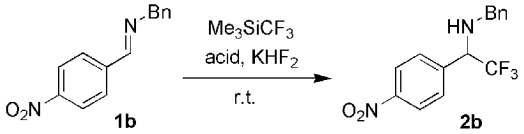
Because optimal conditions require expensive triflic acid and an excess amount of the silane, we felt that cheaper protocols with the use of TFA (Table 1, Entries 3 and 4) could also be evaluated upon studying trifluoromethylation of more active imines.

A variety of imines were involved in the trifluoromethylation reaction with Me_3SiCF_3 (Table 2). Imines bearing electron-rich aromatic rings at the carbon atom turned out to be most reactive and furnished products in high yield within 3 h in the presence of TFA.

Importantly, acid-sensitive furan and acetal fragments are tolerated under the reaction conditions (Table 2, Entries 4, 9, 13). Substrates bearing benzyl, alkyl, cycloalkyl, and allyl substituents at the nitrogen atom also work well in this process. However, the benzhydryl group tends to decrease the product yield (Table 2, Entry 9 vs. Entries 10–12). The imine derived from glycine afforded the corresponding trifluoromethyl derivative, albeit in moderate yield (Table 2, Entry 22), which may be associated with the electron-withdrawing effect of the methoxycarbonyl group. It should be pointed out that substrate may contain an unprotected hydroxy group both in the aromatic ring (Table 2, Entries 23 and 24) and in the substituent at the nitrogen atom, although in the latter case the yield was modest (Table 2, Entries 25 and 26).

Imines derived from tertiary and α-branched aliphatic aldehydes were successfully involved in the trifluoromethylation reaction (Table 2, Entries 27 and 28). At the same time, reaction of α-unbranched substrate **1x** under the standard conditions did not give the expected product. Instead, we isolated amine **3**, which is formed through initial aldolization, followed by trifluoromethylation of the α,β-unsaturated imine [Equation (3)].

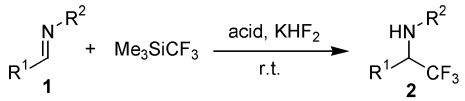
Table 1. Trifluoromethylation of imine **1b**.



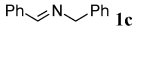
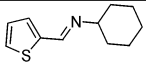
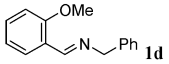
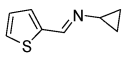
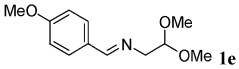
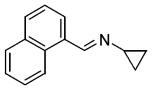
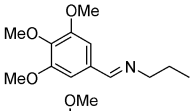
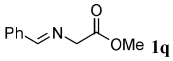
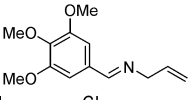
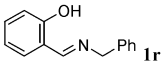
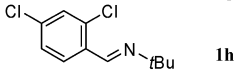
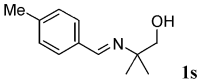
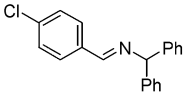
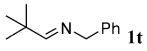
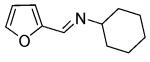
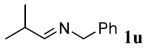
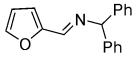
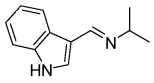
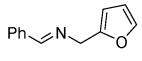
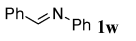
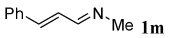
	Solvent	Acid	Acid [equiv.]	KHF_2 [equiv.]	Silane [equiv.]	Time [h]	Yield of **2b** [%][a]
1	DMF	TFA	1.25	0.75	1.5	1	–
2	MeCN	TFA	1.25	0.75	1.5	15	69
3	MeCN	TFA	1.5	1	2	15	71
4	MeCN/DMF (3 equiv.)	TFA	1.25	0.75	1.5	3	48
5	MeCN	TfOH	1.6	1.5	3	24	63
6	DMF	TfOH	1.25	0.75	1.5	24	53
7	MeCN/DMF (3 equiv.)	TfOH	1.6	1.5	3	24	83

[a] Isolated yield.

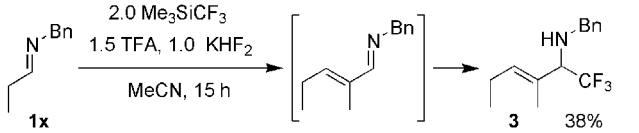
Table 2. Trifluoromethylation of aldimines.



Method	Me_3SiCF_3	Acid	KHF_2	Solvent	Time [h]
A	1.5	1.25 TFA	0.75	MeCN/DMF (3 equiv.)	3
B	2.0	1.5 TFA	1.0	MeCN	15
C	3.0	1.6 TfOH	1.5	MeCN/DMF (3 equiv.)	18

Entry	Imine	Method	Yield of **2** [%][a]	Entry	Imine	Method	Yield of **2** [%][a]
1	 **1c**	A	90	16	 **1n**	A	82
2	 **1d**	A	80	17	 **1o**	A	50
				18		B	63
				19		C	66
3	 **1e**	A	75	20	 **1p**	B	86
4		C	86				
5	 **1f**	A	90	21	 **1q**	B	50
				22		C	60
6	 **1g**	A	81	23	 **1r**	B	63
				24		C	74
7	 **1h**	B	96	25	 **1s**	B	45
				26		C	47
8	 **1i**	B	67	27	 **1t**	A	90
9	 **1j**	A	75	28	 **1u**	A	82
10	 **1k**	A	63	29	 **1v**	B	23
11		B	65	30		C	20
12		C	70				
13	 **1l**	B	88	31	 **1w**	C	70
14	 **1m**	A	65[b]				
15		B	62[b]				

[a] Isolated yield. [b] The product of the trifluoromethylation of cinnamaldehyde (ca. 20%) was also formed.

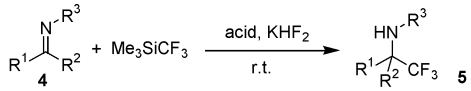


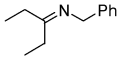
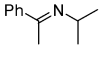
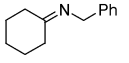
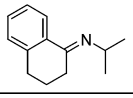
(3)

Several ketimines were also tested in the trifluoromethylation process, and the corresponding products with a four-substituted carbon atom were produced in reasonable yields (Table 3). This is the first example of addition of Me_3SiCF_3 to unactivated ketimines.[15]

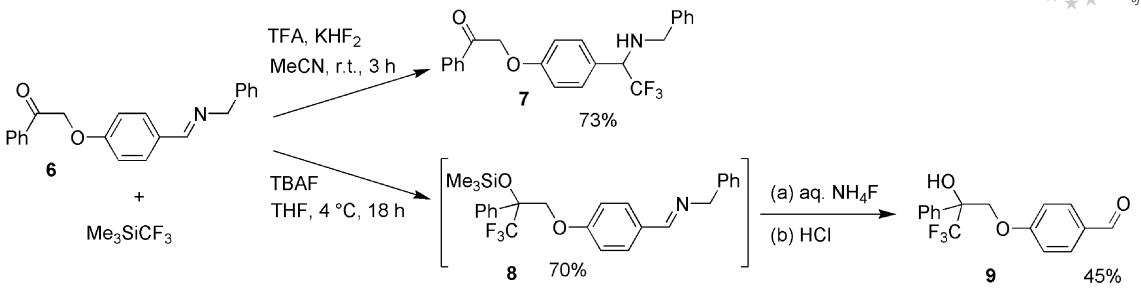
As the carbonyl group is more reactive than the C=N bond in the presence of basic activators for Me_3SiCF_3, it could be expected that in the presence of acid the reactivity order will be reversed. Indeed, trifluoromethylation of imine **6** bearing ketone and azomethine moieties in the presence of TFA/KHF_2 occurred smoothly leading to amino ketone **7**

Table 3. Trifluoromethylation of ketimines.



Entry	Imine	Method	Yield of **5** [%][a]
1	 **4a**	A	75
2	 **4b**	A	67
3		C	68
4	 **4c**	A	62
5	 **4d**	A	68

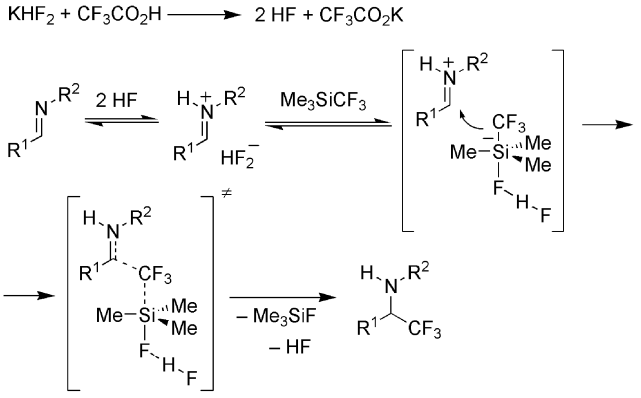
[a] Isolated yield.



Scheme 1. Chemoselective trifluoromethylation.

(Scheme 1).[16,17] In contrast, the reaction mediated by Bu_4NF affected only the keto group to give silyl ether **8** as the initial product. Compound **8** decomposes upon silica gel chromatography, and its yield was determined by NMR spectroscopy. Nevertheless, the desilylation and acidic treatment of a crude sample allowed isolation of aldehyde **9**.

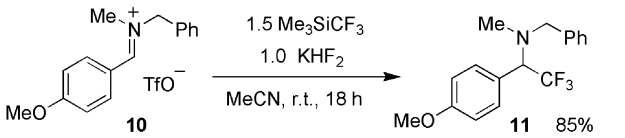
Concerning the mechanism of the trifluoromethylation, we believe that the process is mediated by hydrofluoric acid produced from KHF_2 and TFA (Scheme 2).



Scheme 2. Reaction mechanism.

The interaction of HF with the imine generates an iminium ion and the hydrodifluoride anion, which acts as a Lewis basic activator with respect to the silane. *It seems that concerted transfer of the CF_3 group from the silicon atom to the iminium electrophile takes place.*[18] Otherwise, if the free trifluoromethyl carbanion were generated, it would be readily quenched by the excess amount of TFA.

In accord with this mechanism is the observation that the reaction proceeds faster with more basic imines. To gain support for the ability of the hydrodifluoride anion to activate the silane, we carried out the reaction of preformed *N*-methyl-*N*-benzyliminium salt **10** with Me_3SiCF_3 in the presence of KHF_2 in acetonitrile and obtained expected product **11** in 85% yield [Equation (4)].



(4)

Conclusions

In summary, we demonstrated for the first time that nucleophilic trifluoromethylation can be performed under acidic conditions. The concerted transfer of the CF_3 carbanion from the silicon atom to the iminium electrophile is believed to be responsible for the efficiency of the reaction. This methodology broadens significantly the scope of the trifluoromethylation of the C=N bond, and it offers a new selectivity profile for the application of the Ruppert–Prakash reagent.

Experimental Section

Representative Procedure

Method A: Trifluoroacetic acid (96 μL, 1.25 mmol) was added to a mixture of imine (1 mmol) and KHF_2 (59 mg, 0.75 mmol) in acetonitrile (2 mL) and DMF (232 μL, 3 mmol) at 0 °C, and the suspension was stirred for 5 min. Me_3SiCF_3 (221 μL, 1.5 mmol) was added, the cooling bath was removed, and the mixture was stirred for 3 h at room temperature. For the workup, saturated aqueous Na_2CO_3 (0.5 mL) was added dropwise, and the mixture was stirred for an additional 2 min, diluted with water (7 mL), and extracted with diethyl ether/hexane (1:1, 3 × 5 mL). The combined organic phase was filtered through Na_2SO_4 and concentrated under vacuum, and the crude product was chromatographed on silica gel.

Supporting Information (see footnote on the first page of this article): Experimental procedures and spectroscopic data for all compounds.

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[15] The reaction of highly electrophilic α,α-difluoro-substituted *N*-arylketimine with Me_3SiCF_3 in the presence of Me_4NF has recently been reported, see ref.[13d]
[16] The contribution of attack on the keto group did not exceed 1%, as judged by analysis of crude NMR spectra.
[17] In fact, even benzaldehyde was found to be unreactive under the conditions of methods B and C. However, by using method A, trifluoromethylation occurred slowly with 20% conversion to the corresponding 2,2,2-trifluoro-1-phenylethanol.
[18] The concerted transfer of the C_6F_5 group from the silicon atom to the iminium cation was previously considered computationally, see ref.[14b]

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