ORGANIC LETTERS

2006
Vol. 8, No. 16
3589−3592

Preparation of Tri- and Difluoromethylated Amines from Aldimines Using (Trifluoromethyl)trimethylsilane

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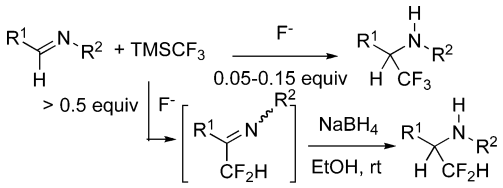
Received June 2, 2006

ABSTRACT



Addition of a trifluoromethyl group into aldimines was accomplished using (trifluoromethyl)trimethylsilane with tetraalkylammonium fluorides as initiators, and the resulting adducts were converted to difluoromethylated imines in the presence of excess fluoride. The imines were reduced to difluoromethylated amines using sodium borohydride.

Synthesis of tri- and difluoromethylated amines is important because of their attractive properties in biological and medicinal chemistry.[1] One of the methods to synthesize trifluoromethylated amines is by the addition of the CF_3 moiety to imines. We have reported that (trifluoromethyl)-trimethylsilane ($TMSCF_3$) is an effective reagent for nucleophilic trifluoromethylation,[2] and its applications have been widely studied.[3] However, in some studies, it was reported that $TMSCF_3$ does not work well for N-unactivated imines, except in the case of reactive azirines,[4] nitrones,[5] and *N*-(*tert*-butylsulfinyl)imines.[6] In one study reported by Blazewski et al., the addition of the CF_3 group to N-unactivated imines has been carried out using $TMSCF_3$.[7] They used TMS-imidazole as an additive to trap the unstable intermediate and obtained the trifluoromethylated amines only in moderate yields. Yokoyama and Mochida have also reported the nucleophilic addition of the CF_3 moiety into N-unactivated imines, using $PhSCF_3$ and Et_3GeNa.[8]

The introduction of the CF_2H group into carbonyl compounds with (difluoromethyl)dimethylphenylsilane (Me_2PhSi-CF_2H) was reported by Hagiwara and Fuchikami.[9] It was difficult to break the $Si-CF_2H$ bond because of its shorter bond length than that of the $Si-CF_3$ bond, and the reactions needed harsher conditions. However, no direct addition to

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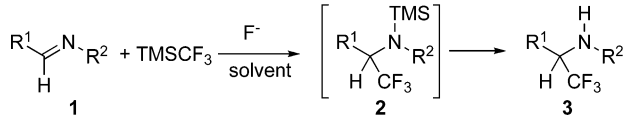
10.1021/ol061357w CCC: $33.50 © 2006 American Chemical Society
Published on Web 07/11/2006

imines was reported. Recently, our group reported the introduction of the CF_2H group into alkyl halides (by nucleophilic substitution) and carbonyl compounds (by addition) using difluoromethyl phenyl sulfone or bromodifluoromethyl phenyl sulfone as a difluoromethyl anion equivalent.[10a−c] More recently, Li and Hu have developed[10d] the addition of the CF_2H group into *tert*-butylsulfinylimines in high diastereoselectivity. On the other hand, there are few methods available to transform a CF_3 group into a CF_2H moiety. Uneyama et al. reported defluorination from trifluoromethyl ketones to form difluoroenol silyl ethers by either electrochemical reduction[11] or reduction with Mg(0)[12] in the presence of TMSCl. We have optimized the reaction conditions further, for successful transformation of difluoroenol silyl ethers to difluoromethyl ketones.[13] These reactions have also been applied to trifluoromethylated imines[14] and arenes.[15] Other methods to prepare difluoromethylenolates include the reaction of trifluoromethyl ketones with dimethyl-(phenyl)silyllithium[16] and trifluoromethyl alcohols with butyllithium.[17] Furthermore, 1,1-bis(dimethylamino)-2,2,2-trifluoroethane can be converted to *N*,*N*-dimethyldifluoroacetamide using *n*-butyllithium,[18] and trifluoromethylated pyridines can be converted to the corresponding difluoromethylated pyridines by 1,8-diazabicyclo[5,4,0]undece-7-ene (DBU).[19] Herein, we report a simple method for the introduction of the CF_3 moiety into imines using $TMSCF_3$ and further conversion of the CF_3 group to CF_2H- via a HF elimination and reduction sequence.

The reaction of benzylideneaniline **1a** with $TMSCF_3$ was carried out using tetrabutylammonium triphenyl-difluorosilicate (TBAT) in THF at room temperature. The formation of trifluoromethylated amine **2a** was confirmed by ^1H and ^{19}F NMR in high yield (Table 1, entry 1). The reactions were

Table 1. Modification of Reaction Conditions for the Introduction of CF_3^- into Imines



1 **2** **3**

	1	R^1	R^2	F^-	solvent	**2**[a] (%)	**3**[a] (%)
1	**1a**	Ph	Ph	TBAT	THF	92	–
2	**1a**	Ph	Ph	TBAT	DMF	75	–
3	**1a**	Ph	Ph	TMAF	THF	72	12
4	**1a**	Ph	Ph	CsF	THF	25	–
5	**1a**	Ph	Ph	CsF/Ph_3SiF	THF	25	11
6	**1b**	Ph	4-MeO-Ph	TBAT	THF	86 (59[b])	–
7	**1b**	Ph	4-MeO-Ph	TMAF	THF	(21)	(19)

[a] Yields were estimated by ^1H NMR of reaction crudes. Isolated yields after aqueous workup are shown in parentheses. [b] A mixture with Ph_3SiF.

carried out with **1** (1 mmol) and F^- sources (0.15 mmol) in 5 mL of solvent at room temperature for 1 h.

This is the first example of the introduction of the CF_3 group into N-unactivated imines in a simple and straightforward manner. It was confirmed that DMF could be used as a solvent (Table 1, entry 2) and also that tetramethylammonium fluoride (TMAF) could be used as an initiator (Table 1, entry 3). However, CsF did not work as an initiator (Table 1, entry 4) nor did fluorotriphenylsilane have any effect in promoting the reaction (Table 1, entry 5). The use of the tetraalkylammonium salts is important to accomplish the reactions. In the case of imine **1b**, TMS-protected intermediate **2b** was stable enough to be isolated (Table 1, entries 6 and 7).

Subsequently, we applied the methodology to other imine derivatives (Table 2). The reactions were carried out with **1**

Table 2. Introduction of CF_3^- into Various Imines

	1	R^1	R^2	TBAT (equiv)	**3** (%)[a]
1	**1a**	Ph	Ph	0.15	75
2	**1b**	Ph	4-MeO-Ph	0.15	72
3	**1c**	4-Me-Ph	Ph	0.15	46
4	**1d**	4-MeO-Ph	Ph	0.15	38
5	**1e**	4-Cl-Ph	Ph	0.05	54
6	**1f**	4-F-Ph	Ph	0.05	67
7	**1g**	4-Br-Ph	Ph	0.05	50
8	**1h**	2,4-Cl_2-Ph	Ph	0.05	77
9	**1i**	2-F-Ph	Ph	0.05	74
10	**1j**	2-Br-Ph	Ph	0.05	83
11	**1k**	*c*-C_6H_{11}	Ph	0.05	47
12	**1l**	*t*-Bu	Ph	0.05	trace

[a] Isolated yields.

(1 mmol), $TMSCF_3$ (213 mg, 1.5 mmol), and TBAT in 5 mL of THF at room temperature for 1 h. Benzylideneanilines without any substituent on the aryl rings or with halogens on them showed moderate to good yields. However, electron-donating substituents on R^1 resulted in lower yields (Table 2, entries 3 and 4). Two kinds of aliphatic aldimines were tested, and imine **1k** gave trifluorinated amine **3k** in moderate yield (Table 2, entry 11); however, imine **1l** did not work well (Table 2, entry 12).

Surprisingly, when the trifluoromethylation of 4-Cl derivative **1e** was carried out with 0.15 equiv of TBAT, the

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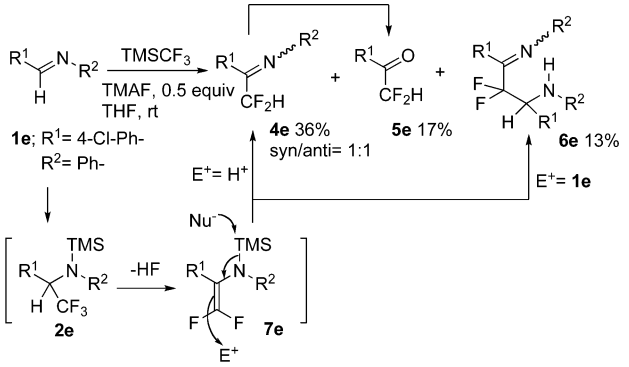
CF_2H moiety was identified in the ^1H and ^{19}F NMR of the crude product. We investigated this product carefully and optimized the reaction conditions. Difluoromethyl imines **4e** were obtained as a 1:1 mixture of syn and anti isomers by the reaction of **1e** and $TMSCF_3$ with 0.5 equiv of TMAF. Some of the imine **4e** was hydrolyzed to the corresponding difluoromethyl ketone **5e** during the workup and on purification over silica gel column chromatography. The plausible mechanism for the formation of difluoromethylated imine is shown in Scheme 1. The elimination of HF from TMS-

Scheme 1

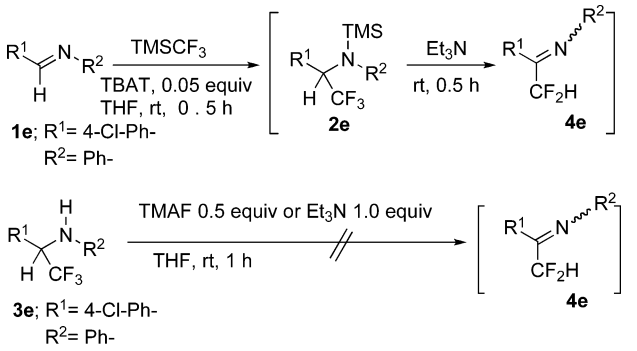


protected amine **2e** can give rise to the difluoroenamine intermediate **7e**. Subsequently, the nucleophile (F^-) can attack the Si atom of the TMS group of **7e**, and the resulting species react with a proton to give the difluoromethylimine **4e** or with unreacted starting material **1e** to give the dimer product **6e**. The preparation of trimethylsilylated difluoroenamines, such as the intermediate **7e**, was reported earlier by Uneyama et al.[14] They isolated the difluoroenamines and investigated the reactions with some nucleophiles (PhLi, ROH, F^-) and electrophiles (H^+, RCHO, R−I, PhSCl, PhSeF). Under our reaction conditions, nucleophile F^- is already present in the reaction media; therefore, the conversion of enamine **7e** to difluoromethylimine **4e** takes place in situ.

The elimination of HF from **2e** needs a base, and the actual species which is acting as a base in the reaction medium must be F^-. To confirm the reaction pathway, we studied some reactions as shown in Scheme 2. The reaction of imine **1e** with $TMSCF_3$ using 0.05 equiv of TBAT was carried out in THF at room temperature for 0.5 h, followed by the addition of 1.0 equiv of triethylamine. The mixture was stirred for another 0.5 h. The formation of the CF_2H− moiety was confirmed by ^1H and ^{19}F NMR. On the other hand, treatment of trifluoromethylated amine **3e** with 0.5 equiv of TMAF or 1.0 equiv of triethylamine resulted in no reaction. According to these results, the actual species, which is converted to difluoroenamine **7**, is not free amine **4** but the TMS-protected amine **2**.

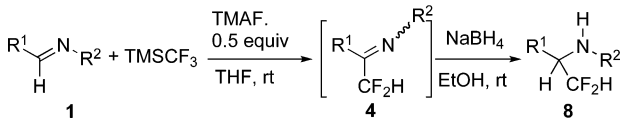
It was difficult to isolate difluoroimines **4** in high yield because of their reactivity toward water and silica gel. Therefore, we directly reduced the intermediate imines to the corresponding difluoromethylamines by $NaBH_4$. This

Scheme 2



gave difluoromethylated amines **8** in moderate to good yields (Table 3). The reactions were carried out with **1** (1.0 mmol),

Table 3. Direct Preparation of Difluorinated Amines from Imines



	1	R^1	R^2	TMAF (equiv)	8 (%)[a]	3 (%)[a]
1	**1a**	Ph	Ph	0.5	62	–
2	**1b**	Ph	4-MeO-Ph	0.5	37	–
3	**1e**	4-Cl-Ph	Ph	0.5	78	–
4	**1f**	4-F-Ph	Ph	0.5	79	–
5	**1g**	4-Br-Ph	Ph	0.5	63	–
6	**1h**	2,4-Cl_2-Ph	Ph	0.5	58	6
7	**1i**	2-F-Ph	Ph	1.0	35	23
8	**1j**	2-Br-Ph	Ph	1.0	trace	46
9	**1k**	*c*-C_6H_{11}	Ph	0.5	0	34
10	**1l**	*t*-Bu	Ph	0.5	0	23[b]

[a] Isolated yields. [b] $(CH_3)_3CCH_2NHPh$, which was the reduction product of **1l**, was also obtained in 26% yield.

$TMSCF_3$ (213 mg, 1.5 mmol), and TMAF in 5 mL of THF at room temperature for 1 h, followed by treatment with $NaBH_4$ (757 mg, 20 mmol) in 10 mL of EtOH at room temperature for 1 h.

In the case of 2-substituted phenyl imines such as **1i** and **1j**, the conversion of the CF_3 group into the CF_2H moiety was suppressed even with 1.0 equiv of TMAF, and trifluoromethylated amines **3i** and **3j** were recovered (Table 3, entries 7 and 8). We also attempted to extend this reaction to aliphatic imines; however, the conversion to the CF_2H amine did not occur with these substrates (Table 3, entries 9 and 10).

In summary, $TMSCF_3$ can be used for the introduction of the CF_3 moiety into N-unactivated imines using tetraalkylammonium fluorides as initiators. The reaction can be carried out at ambient temperature, is easy to handle, and gives the trifluoromethylated amines in moderate to good yields. Furthermore, difluoromethylated amines can be prepared

directly from imines and $TMSCF_3$ using half a molar amount of TMAF, followed by the reduction with $NaBH_4$. The mechanism involves the elimination of HF from TMS-protected trifluoromethylated amines to provide the difluoromethylimine intermediate (through the difluoromethyl enamine), which is reduced by sodium borohydride to the difluoromethylated amine product.

Acknowledgment. Support of our work in part by the Loker Hydrocarbon Research Institute is gratefully acknowledged. R. Mogi thanks Kanto Denka Kogyo Co., Ltd. for the financial support and sponsorship.

Supporting Information Available: General experimental paragraph; experimental procedures for the preparation of **3** and **8**; ^{1}H, ^{19}F, ^{13}C NMR and mass characterization data of the isolated products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL061357W