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Nucleophilic difluoromethylation of *N*,*N*-acetals with $TMSCF_2SO_2Ph$ reagent promoted by trifluoroacetic acid: A facile access to α-difluoromethylated tertiary amines

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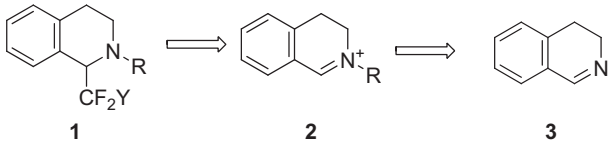
ABSTRACT

A protocol for the synthesis of difluoromethylated tertiary amines by nucleophilic difluoromethylation of *N*,*N*-acetals using $TMSCF_2SO_2Ph$ reagent is developed. The reaction proceeds smoothly in 1,4-dioxane using K_2CO_3 as the initiator. A key feature of the reaction is that the in situ generated iminiums (from *N*,*N*-acetals and CF_3COOH) could be fluoroalkylated in an efficient way.

1. Introduction

Fluoroalkyl amines are of great interest in bioorganic and medical chemistry research due to the profound change of the basicity of the amine functionality imposed by the fluoroalkyl group [1–3]. Since the first nucleophilic synthesis of enantiomerically pure α-trifluoromethylated primary amines with Ruppert–Prakash reagent ($TMSCF_3$) in 2001 [4,5], numerous works have been devoted to developing efficient methods for the synthesis of structure-diverse fluoroalkylated primary and secondary amines [6–8]. Only in recent years, attention has been paid to the direct synthesis of fluoroalkylated tertiary amines by nucleophilic fluoroalkylation of iminium cation intermediates [6]. The commonly used methods for the generation of iminum cations in fluoroalkylation reactions include: (1) alkylation of imines [9], (2) protonation of enamines [10], (3) condensation of aldehydes and *N*-trimethylsilylamines in the presence of TMSOTf [9], and (4) oxidation of tertiary amines [11,12]. Dilman and co-workers have exploited the first three methods for transferring trifluoromethyl or other fluorinated groups to iminium cations [9,10]. The research groups led by Qing [11] and Li [12] have developed an oxidative trifluoromethylation of tertiary amines via iminium cation intermediates based on the fourth method [11,12]. However, all the research has focused on the synthesis of trifluoromethylated or perfluorinated tertiary amines. The synthesis of difluoromethylated tertiary amines using various difluoromethylating agents [13–15] is also of great importance, since CF_2H group could act as lipophilic hydrogen bond donor and alcohol isostere [16,17]. Recently, we reported the difluoromethylation of C=N bonds in heterocycles under the activation of alkylation reagents (Eq. (1)), which can be applicable for the synthesis of difluoromethylated tertiary amines such as **1** [18]. As our continuing effort on the synthesis of potentially useful difluoromethylated tertiary amines such as **4**, we investigated the use of *N*,*N*-acetals **6** as iminium cation precursors (Eq. (2)). In this article, we wish to report our results on the difluoromethylation of *N*,*N*-acetals promoted by Me_3SiCl or trifluoroacetic acid.



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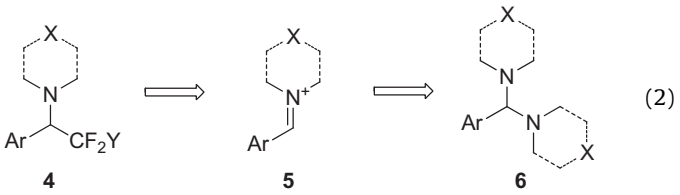
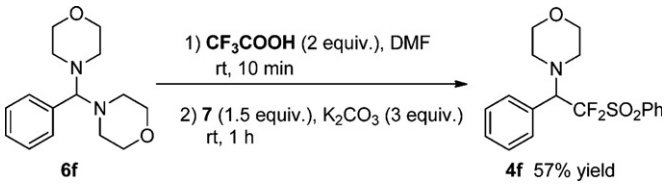




Scheme 1.

2. Results and discussion

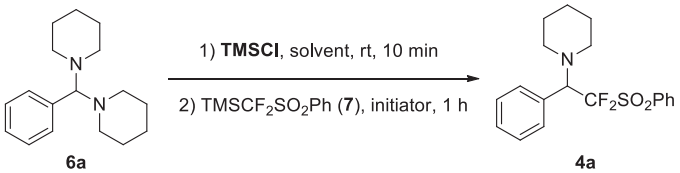
At the onset of our investigation, we synthesized a series of *N*,*N*-acetals **6** by condensation of aromatic aldehydes with dialkyl amines, such as piperidine, morpholine and dimethylamine according to known methods [19–21]. All the *N*,*N*-acetals were purified by recrystallization. With a series of *N*,*N*-acetals in hand, we carried out the nucleophilic (phenylsulfonyl)difluoromethylation of *N*,*N*-acetal **6a** (derived from benzaldehyde and piperidine) with $TMSCF_2SO_2Ph$ (**7**) (Table 1). It was found that no expected fluoroalkylation reaction took place in the presence of a Lewis base initiator in DMF (entry 1). Some previous reports have pointed out that a Lewis acid such as trimethylsilyl chloride (TMSCl) could promote the formation of iminiun cation species from *N*,*N*-acetals [21–23]. Therefore, we tried the fluoroalkylation using TMSCl as an activator. After *N*,*N*-acetal **6a** was treated with TMSCl (1.5 equiv.) in dimethoxyethane (DME) at room temperature for 10 min, subsequent addition of $TMSCF_2SO_2Ph$ (**7**) (1.5 equiv.) and K_2CO_3 (1.5 equiv.) resulted in the formation of the desired product **4a** in 57% yield (entry 2). Inspired by this result, we further optimized the reaction parameters such as solvents, initiators and reactant ratios (entries 2–8). It was found that DME was the optimal solvent and a combination of **6a**, **7**, TMSCl and K_2CO_3 in a ratio of 1:1.5:2:3 gave **4a** in a good yield (84%, see entry 3).

However, in the case of *N*,*N*-acetal **6f** derived from morpholine, no expected product was detected using the optimized conditions (as shown in entry 3, Table 1). It was reported that a similar alkylation of *N*,*N*-acetal **6f** in the presence of TMSCl was also not efficient [21]. We then aimed at seeking a more effective activator (than TMSCl) to ensure the efficient formation of the iminium species from **6f**. After a screening of several Brønsted acids, trifluoroacetic acid (TFA) was found to be the optimal acid due to its strong acidity and low oxidizing ability. Under the activation of TFA, the difluoromethylation of *N*,*N*-acetal **6f** in DMF gave the fluoroalkylated amine **4f** in 67% yield using the above optimized reactant ratio (Scheme 1). Moreover, TFA proved to be a general activation reagent for all *N*,*N*-acetals tested, including morpholine- and piperidine-derived ones.

A further optimization of the reaction conditions using 3 equivalents of K_2CO_3 showed that the reaction between piperidine-derived *N*,*N*-acetal **6a** and **7** was significantly influenced by both solvent and the reactant ratio (Table 2). When 1.5 equivalents of **7** and 2 equivalents of TFA were employed and among several solvents that were tested, the reaction in 1,4-dioxane gave much higher yield (69%) (entries 1–4). Further studies showed that a combination of 2 equivalents of **7** and 1.5 equivalents of TFA gave **4a** in excellent yield (92%) (entry 8). However, the Lewis base initiator had little influence on the reaction, and both K_2CO_3 and KF gave similar results (entries 4–7). To identify the reactive intermediates in this reaction, the reaction mixture of *N*,*N*-acetal **6a** with TFA was characterized by NMR. When **6a** was treated with 1.5 equivalents of CF_3COOH in DMSO-d_6 at room temperature for 10 min, the ^1H NMR showed the disappearance of the peak corresponding to the PhC–H proton of **6a** ($\delta = 3.63$) and the appearance of a new peak at $\delta = 10.06$, which was assigned to the methine proton of the iminium cation **B** [23]. Moreover, the aromatic hydrogens shifted downfield (from $\delta = 7.15–7.40$ to $\delta = 7.60–7.80$), which was in accordance with the deshielding effect caused by the positive charge at the iminium cation. Based on theses findings, the reaction pathway is depicted in Scheme 2.

Using the conditions shown in Table 2, entry 8 as standard, we investigated the difluoromethylation of various *N*,*N*-acetals **6** with reagent **7** (Table 3). In all cases, (phenylsulfonyl)difluoromethylated cyclic and acyclic tertiary amines **4** were obtained in moderate to excellent isolated yields. Both aromatic aldehyde- and heteroaromatic aldehyde-derived acetals (such as **6k**) were found to be viable substrates for the current reaction. In general, the morpholine-derived acetals afforded the products in relatively

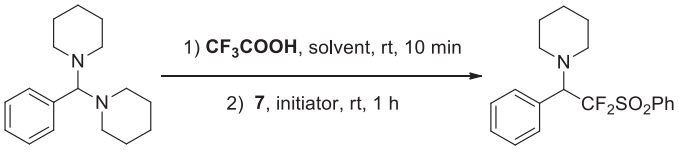
Table 1
Difluoromethylation of *N*,*N*-acetal **6a** promoted by TMSCl.



Entry	Solvent	Initiator	**6a**:7:TMSCl:initiator	Yield (%)[a]
1	DMF	K_2CO_3, NaOAc, or KF	1:1.5:0:1.5	0
2	DME	K_2CO_3	1:1.5:1.5:1.5	57
3	**DME**	**K_2CO_3**	**1:1.5:2:3**	**84**
4	CH_2Cl_2	K_2CO_3	1:1.5:2:3	0
5	THF	K_2CO_3	1:1.5:2:3	45
6	DMF	K_2CO_3	1:1.5:2:3	54
7	DME	NaOAc	1:1.5:2:3	46
8	DME	KF	1:1.5:2:3	77

[a] Determined by ^{19}F NMR.

Table 2
Difluoromethylation of *N*,*N*-acetal **6a** promoted by CF_3COOH.



Entry	Solvent	Initiator	**6a**:7:TFA:initiator	Yield (%)[a]
1	DMF	K_2CO_3	1:1.5:2:3	52
2	DMSO	K_2CO_3	1:1.5:2:3	32
3	CH_3CN	K_2CO_3	1:1.5:2:3	9
4	1,4-Dioxane	K_2CO_3	1:1.5:2:3	69
5	1,4-Dioxane	KF	1:1.5:2:3	69
6	1,4-Dioxane	K_2CO_3	1:2:2:3	86
7	1,4-Dioxane	KF	1:2:2:3	82
8	**1,4-Dioxane**	**K_2CO_3**	**1:2:1.5:3**	**92**

[a] Determined by ^{19}F NMR.