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Graphical Abstract

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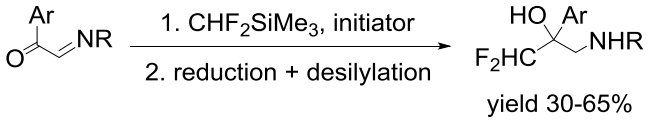

Nucleophilic addition of (difluoromethyl)trimethylsilane to selected α-imino ketones and aryl diketones

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Keywords: (difluoromethyl)trimethylsilane, α-imino ketones, diketones, difluoromethylation, β-amino alcohols, 1,2-diols

ABSTRACT

Chemoselective addition of (difluoromethyl)trimethylsilane (CHF_2SiMe_3) to the carbonyl bond of aryl glyoxal derived α-imino ketones, and selected diaryl 1,2-diketones were studied in the presence of initiators, such as potassium *tert*-butoxide or cesium fluoride. Subsequent reduction of the obtained α-imino alcohols and α-hydroxy ketones with sodium borohydride gave the expected 2-amino 1-(difluoromethyl)alcohols and (difluoromethyl)-1,2-diols respectively in moderate to good yields. High *de* values were observed for the reduction of α-(difluoromethyl)-α-hydroxy ketones.

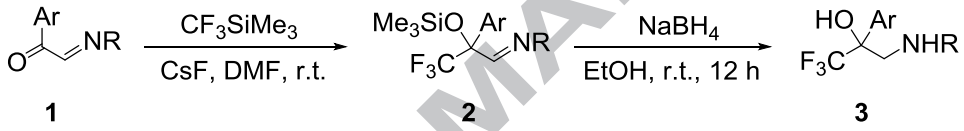
1. Introduction

The development of new methods for the synthesis of organofluorine compounds is currently a challenging topic in current organic chemistry.[1] Special interest is focused on the synthesis of derivatives containing small fluoroalkyl groups (e.g. CF_3, CHF_2).[1] Organic compounds functionalized with these substituents are considered as attractive building blocks and molecules with potential application in the preparation of drugs,[1a,b] agrochemicals[1a] or materials with special properties.[1a] Methods for the incorporation of the CF_3 group into the structure of organic substrates are well known.[1,2] Currently, (trifluoromethyl)trimethylsilane (so-called Ruppert's-Prakash reagent, CF_3SiMe_3) is well known as a universal trifluoromethylating agent.[2] On the other hand, protocols for the incorporation of a CHF_2 group are less well known.[1a,b,2e,3] Recently, (difluoromethyl)trimethylsilane (CHF_2SiMe_3) has been reported as a promising difluoromethylating agent[4] and this reagent has been utilised as a nucleophilic reagent in the reaction with simple carbonyl compounds and activated *N*-sulfinyl imines,[4b,g] as well as with aryl halides, vinyl halides, diazonium salts,[4c,f] and aromatic *N*-oxides.[4e]

β-Amino alcohols are versatile building blocks that have been widely utilised as starting materials for the preparation of more complex molecules and as powerful chiral auxiliaries and/or catalysts in asymmetric synthesis.[5] β-Amino alcohols containing fluoroalkyl groups combine unique physico-chemical and biological properties resulting from the presence of the

fluorinated substituents.[6] Many protocols for the preparation of β-amino α-(trifluoromethyl)alcohols have been described in the literature.[6c] However, methods for the synthesis of β-amino α-(difluoromethyl)alcohols are only scarcely described[7] and the Petasis reaction of 2-hydroxy-3,3-difluoropropanal with arylboronic acids and secondary amines may be considered as the only general method for the preparation of β-amino-α-(difluoromethyl) alcohols.[7d]

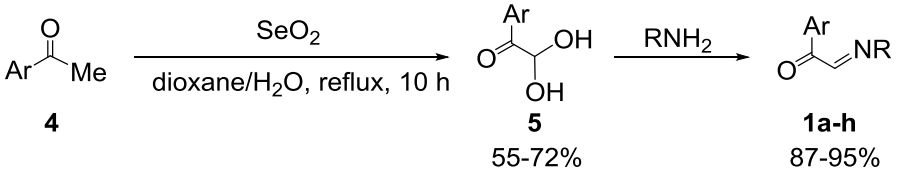
The goal of the present study was the development of a straightforward method to prepare β-amino α-(difluoromethyl)alcohols based on the reaction of α-imino ketones **1** with (difluoromethyl)trimethylsilane. A similar protocol was previously applied by our group for the synthesis of β-amino α-(trifluoromethyl)alcohols.[8] Addition of CF_3SiMe_3 to α-imino ketones **1** led chemoselectively to silyl ethers **2**, which upon treatment with sodium borhydride were converted into the desired trifluoromethylated amino alcohols **3** (Scheme 1).



Scheme 1. Synthesis of β-amino α-(trifluoromethyl) alcohols.

2. Results and discussion

α-Imino ketones **1a-h** were prepared according to the known two-step procedure.[8,9] Oxidation of the appropriate methyl ketones **4** using SeO_2, gave 2,2-dihydroxyethanones **5**, which were converted into α-imino ketones **1a-h** *via* their reaction with the appropriate primary amines (Scheme 2).



Ar = 3,4-$(OCH_2O)C_6H_3$, 3,4-$(MeO)_2C_6H_3$, 4-$MeOC_6H_4$, Ph, 4-BrC_6H_4, 4-$CF_3C_6H_4$, 4-$NO_2C_6H_4$
R = *t*-Bu, *c*Hex

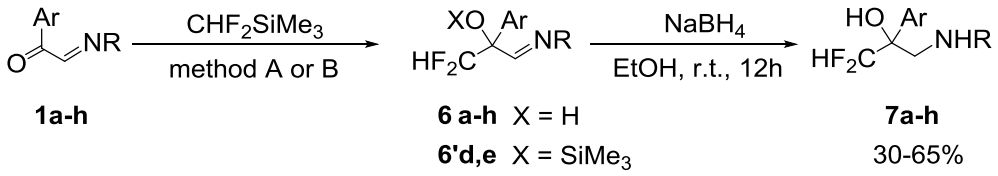
Scheme 2

Due to their stability, substrates **1d** (Ar = Ph) and **1e** (Ar = 4-BrC_6H_4), bearing a bulky *t*-Bu substituent on the nitrogen atom, were selected for preliminary experiments. The

difluoromethylation reactions were performed in the presence of a catalytic amount of cesium fluoride in DMF at room temperature (method A) or alternatively, in the presence of a stoichiometric amount of potassium *tert*-butoxide in THF at –78 °C (method B) (Scheme 3).[10] Based on an earlier protocol,[4b] experiments were carried out using a two-fold excess of (difluoromethyl)trimethylsilane. In analogy to the trifluoromethylation of **1** with CF_3SiMe_3,[8a] addition of CHF_2SiMe_3 to the carbonyl occurred with complete chemoselectivity.

Next, the scope of the reaction was explored with various imino ketones **1**. The initially formed α-hydroxy imines **6** or their silyl ethers **6'** were used without purification for the reduction using sodium borohydride (for compounds of type **6'** simultaneous reduction of the C=N function and desilylation was observed).[11] Yields for the obtained β-amino α-(difluoromethyl)alcohols **7** performed according to method A or method B were comparable (entries 4-7, Table 1). Characteristic splitting patterns resulting from the presence of the CHF_2 group were observed in both ^{1}H- and ^{13}C-NMR spectra of the products. For example, in the case of compound **7d**, the signal for the CHF_2 proton appeared as a dd at 5.70 ppm ($^2J_{H,F(1)}$ = $^2J_{H,F(2)}$ = 55.8 Hz) and a dd originating from the carbon atom was located at 117.6 ppm ($^1J_{C,F(1)}$ = $^1J_{C,F(2)}$ = 247.5 Hz).

We observed that the reaction was strongly dependent on the substituent located on the nitrogen atom and only in the case of substrates bearing *tert*-butyl or cyclohexyl groups was formation of the desired products **6** or **6'** observed. All attempts to utilise other iminoketones **1**, possessing *iso*-propyl, 1-phenylethyl or methoxy substituents, were unsuccessful. We postulate that, under the basic reaction conditions (F^-/DMF, *t*-BuO^-/THF), these less stable substrates **1** underwent decomposition leading to the formation of complex reaction mixtures. The substituent attached to the aromatic ring in substrates **1** also influenced the observed yields and better results were observed for substrates bearing electron-donating groups on the phenyl ring (Table 1). It is worth emphasising, that similar reactions of **1** with (trifluoromethyl)trimethylsilane led to the expected products in higher yields irrespective of the substituent at the nitrogen atom.[8] This observation could be explained by the higher reactivity of CF_3SiMe_3 towards electrophiles in comparison with CHF_2SiMe_3.[4b] Additionally, more drastic conditions were required for the activation of CHF_2SiMe_3.



Scheme 3. Chemoselective additions of (difluoromethyl)trimethylsilane to α-iminoketones **1**

Table 1 Nucleophilic difluoromethylation of α-imino ketones **1a-h**

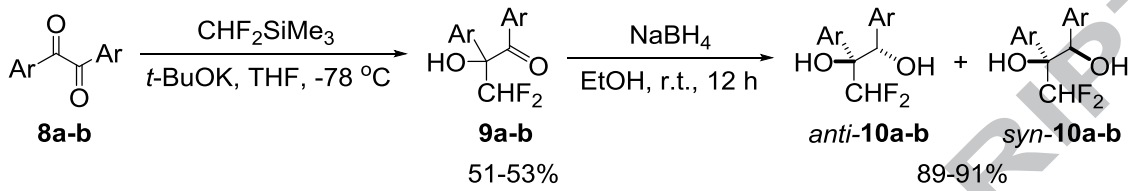
Entry	Substrate	Method[a]	X	Ar	R	Yield of 7 (%)[b]
1	**1a**	B	H	3,4-$(OCH_2O)C_6H_3$	*t*-Bu	65
2	**1b**	B	H	3,4-$(MeO)_2C_6H_3$	*t*-Bu	55
3	**1c**	B	H	4-$MeOC_6H_4$	*t*-Bu	48
4	**1d**	A	$SiMe_3$	Ph	*t*-Bu	65
5	**1d**	B	H	Ph	*t*-Bu	63
6	**1e**	A	$SiMe_3$	4-BrC_6H_4	*t*-Bu	45
7	**1e**	B	H	4-BrC_6H_4	*t*-Bu	43
8	**1f**	B	H	4-$F_3CC_6H_4$	*t*-Bu	63
9	**1g**	B	H	4-$NO_2C_6H_4$	*t*-Bu	30
10	**1h**	B	H	Ph	*c*Hex	43

[a]Method **A**: CsF (cat.), DMF, r.t, 12 h; Method **B**: *t*-BuOK (2.0 equiv.), THF, –78 °C, 12 h

[b]Total yield for the two-step protocol (**1** → **7**)

In an extension of this study, addition of (difluoromethyl)trimethylsilane to symmetrical, diaryl 1,2-diketones **8** was performed under the optimized reaction conditions.[10] Benzil (**8a**) and phenanthrenequinone (**8b**) were reacted with CHF_2SiMe_3 to give the α-hydroxy ketones **9** as the sole products in moderate yields (Scheme 4, Table 2). Remarkably, experiments performed with two equivalents of the difluoromethylating agent resulted in exclusive formation of the 1:1 adducts. Upon treatment with $NaBH_4$, the obtained α-hydroxy ketones **9** were reduced to the corresponding 1,2-diols **10** in high yields.[11] In the case of **9a** a mixture of both isomers was obtained (*dr* 88:12), whereas the reduction of **9b** led to the formation of a single diastereoisomer. Unfortunately crystals of **10a**,**b** and their 1,3-dioxolanone derivatives were not suitable for X-ray analysis and the *syn*/*anti* configuration of the major products was thus not established. The structure of the obtained products **10a**,**b** was tentatively assigned as

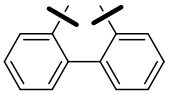
the *anti*-isomer based on the results of analogous reductions reported for the α-hydroxy-α-(trifluoromethyl) ketones.[12]



Scheme 4. Chemoselective addition of (difluoromethyl)trimethylsilane to aryl diketones **8a-b**

Table 2

Nucleophilic addition of (difluoromethyl)trimethylsilane to symmetrical aryl diketones **8a-b**

Substrate	**Ar, Ar**	**9**	**10**	
		Yield (%)	***de*[a]**	**Yield (%)**
8a	Ph, Ph	53	76	55 (89)[b]
8b		51	>99	91

[a]On the basis of the ^{19}F NMR spectra of crude reactions mixtures.

[b] Yield of pure *anti* diastereoisomer of **10a-b**; in parentheses total yield of both isomers.

4. Conclusions

A new, straightforward method for the synthesis of a series of new 2-amino-1-(difluoromethyl)alcohols **7** and 1-(difluoromethyl)-1,2-diols **10**, based on relatively inexpensive and readily accessible starting materials was described. In the case of amino alcohols **7**, the presented method complements an already reported protocol based on the Petasis reaction. In most of the described cases, products **7** and **10** were obtained in satisfactory yields. They can be considered as new, attractive building blocks for the synthesis of more complex fluorinated compounds. To the best of our knowledge, this is the first protocol, which provides access to difluoromethylated diols *via* the selective nucleophilic difluoromethylation of 1,2-diketones. This compares well to a recently published patent leading to azido-functionalized diols containing the CHF_2 moiety.[13]

5. Acknowledgements

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10. a) General procedure for the reactions of α-imino ketones **1** and 1,2-diketones **8** with (difluoromethyl)trimethylsilane. **Method A**: The appropriate α-imino ketone **1** (1.0 mmol) dissolved in anhydrous DMF (~1 mL) was placed in a dry two-neck flask, equipped with a septum and an argon balloon. A catalytic amount of freshly dried CsF and CHF_2SiMe_3 (250 mg, 2.0 mmol) were added at room temperature. The reaction mixture was left for 24 h and quenched with H_2O (~2 mL). The solution was extracted with CH_2Cl_2 (4 x 5 mL), and the organic layers combined and dried over anhydrous Na_2SO_4. After filtration, the solvents were removed under reduced pressure. **Method B**: The appropriate substrate **1** or **8** (1.0 mmol) was dissolved in anhydrous THF (~5 mL) and placed in a dry two-neck flask, equipped with a septum, an argon balloon and a tube filled with anhydrous $CaCl_2$. Then reaction flask was cooled to –78 ºC. Next, *t*-BuOK (220 mg, 2.0 mmol) and CHF_2SiMe_3 (250 mg, 2.0 mmol) were added. The reaction mixture was stirred for 4 h and quenched with H_2O (~4 mL). The solution was extracted with Et_2O (4 x 5 mL). The organic layers were combined and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated. The obtained (difluoromethyl) imino alcohols **6** or their silyl ethers **6′** were used in the next step without purification. (Difluoromethyl)hydroxy ketones **7** were purified by flash column chromatography.

11. General procedure for the reduction of (difluoromethyl)imino alcohols **6**, their silyl ethers **6′** and (difluoromethyl)hydroxyl ketones **9**. Compound **6**, **6′** or **9** (1.0 mmol) was dissolved in EtOH (~5 mL), and $NaBH_4$ (110 mg, 3.0 mmol) was added. The reaction mixture was stirred at room temperature for 12 h. The solvent was then removed under reduced pressure. Next, H_2O (~5 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (4 x 5 mL). The organic layers were combined, dried over anhydrous Na_2SO_4 and the solvent was evaporated. The obtained β-(difluoromethyl)-α-amino alcohols **7** or (difluoromethyl)-1,2-diols **10** were purified by flash column chromatography eluting with hexane/Et_2O 8:2 and/or crystallization from an appropriate solvent.

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