



# Detrifuoroacetylation of 4,4,4-trifluoro-3,3-dihydroxy-2-(hydroxyimino)butan-1-ones as a convenient synthetic strategy for acyl cyanides



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## ABSTRACT

A reaction reinvestigation of fluorinated 1,3-dicarbonyl compounds with NaNO<sub>2</sub> in acidic conditions revealed the formation of corresponding 1,1,1-trifluoro-3-hydroxyimino-butan-2,4-diones which predominantly isolated as hydrates. A novel synthesis of ethoxy-, alkyl-, (het)aryl substituted carbonylcyanides via acid-catalyzed detrifuoroacetylation of obtained 2-hydroxyimino derivatives of 1,3-dicarbonyl compounds was described.

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## 1. Introduction

Trifluoroacetyl group is one of widely used functionalities in organic synthesis and plays a significant role in the construction of fluorinated building blocks, such as enones, 1,3-diketones, heterocyclic derivatives [1]. The electron-withdrawing properties of CF<sub>3</sub> group enhanced the electrophilicity of carbonyl carbon atom thereby promoting the nucleophilic attack by different *N,O,C*-reagents [2]. In contrast to nonfluorinated analogs, the ability of the trifluoromethyl group to stabilize acetals, hydrates or amins is well known for trifluoroacetyl derivatives [3].

The loss of the CF<sub>3</sub>C(O) moiety is usually an unexpected result which is rarely reported in the literature [1b,4]. Recently, much attention has been devoted to detrifuoroacetylation approaches of some 1,1,1-trifluoro-2,4-dione derivatives. Applications of this methodology as a convenient route to *in situ* difluoro(fluoro) enolate generation for reactions with different electrophiles have been reviewed [1b] (Fig. 1). The elimination of the trifluoroacetyl group after functionalization of 1,1,1-trifluoro-2,4-diones has been used in the synthesis of hardly available  $\alpha,\beta$ -unsaturated ketones [4a],  $\gamma$ -nitroketones [4b],  $\alpha$ -diazoketones [4c], *N*-substituted

$\alpha$ -amino esters and  $\alpha$ -aminoketones [4d]. The base or nucleophile action on the trifluoroacetyl derivatives resulting in CF<sub>3</sub>C(O) group elimination is one of the main features in most cases thus far studied.

Among fluorinated 2-functionalized 1,3-dicarbonyl compounds, 2-hydroxyimino derivatives **2** are less studied (Fig. 1) [5]. To the best of our knowledge, only a few reports have been described applications of such derivatives in pyrazoles, [5b–f] benzodiazepines [5e,f] and aminoacids [5g] preparation. In most cases hydroxyimino derivatives **2** have been used without isolation as *in situ* prepared intermediates. From this point, their applications are still limited. It has been mentioned, that some of **2** could not be isolated from the reaction mixture probably due to their low stability [5a,f]. For almost two last decades, only two examples of trifluorinated hydroxyimino derivatives **2** were characterized by IR and <sup>1</sup>H NMR spectra [5f,g].

Hence, our motivation in this work was to explore the peculiarities of trifluorinated 2-hydroxyimino-1,3-dicarbonyl compound preparation and their isolation in pure form, which would provide the opportunities for broad investigation of their properties and applications. Herein, we wish to report on acid-catalyzed detrifuoroacetylation of 4,4,4-trifluoro-3,3-dihydroxy-2-(hydroxyimino)butan-1-ones to yield carbonylcyanides under mild conditions.

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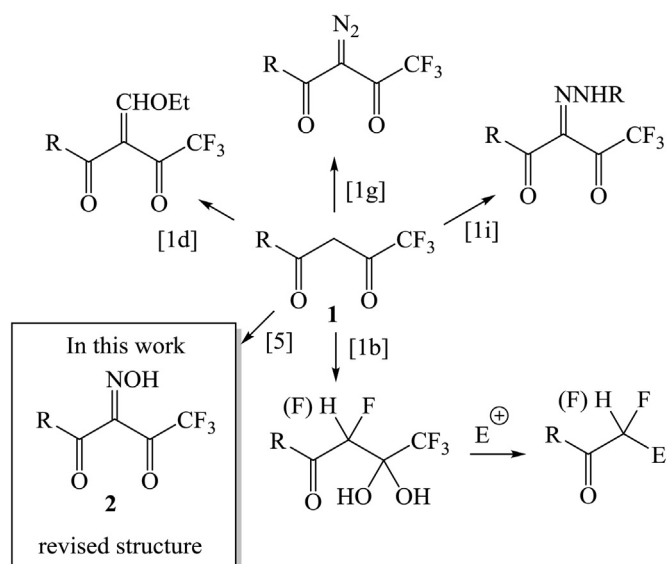


Fig. 1. The examples of 3-functionalized 1,1,1-trifluorobutan-2,4-diones.

## 2. Results and discussion

We commenced our study with the nitrozylation of trifluorinated 1,3-diketones **1a–k** with  $\text{NaNO}_2$  in aqueous  $\text{AcOH}$  accordingly to our previous study. In contrast to non-fluorinated analogs the formation of hydrates **3a–h** of expected 2-hydroxyimino-1,3-diketones **2** was observed (checked by reaction mixture  $^{19}\text{F}$  NMR spectra monitoring) (Scheme 1). In case of trifluoroacetone hydrate **3k** was identified by  $^{19}\text{F}$  NMR spectra of reaction mixture but all attempts of the product **3k** isolation were failed.

The products **3a–h** are white solids, insoluble in chloroform, stable at store for months at ambient conditions. However, to achieve a complete removal of solvent under products **3g,h** isolation the vacuum evaporation on a water bath at  $60^\circ\text{C}$  was required. It resulted in a partial dehydration of obtained products **3g,h** and formation of a mixture containing diketo form **2g,h** in addition to target compounds **3g,h** (see Table 1).

It should be mentioned that the traces of acetic acid in isolated products were identified even after several neutralization steps. Acidic impurities can result in by-products formation under the further transformations of **3** as starting compounds. For example,

in case of the gram scale preparation of **3**, GC–MS analysis of the reaction mixture revealed the formation of non-fluorinated by-products (5–10%) as acyl nitriles and their derivatives. To facilitate the product **3** purification and avoid detrifluoroacetylation process caused by acetic acid we attempted to apply acid with low solubility in organic media.

The use of citric acid (2 equiv) in the reaction of 1,3-dicarbonyl compounds (1 equiv) with  $\text{NaNO}_2$  (1.2 equiv) allowed us to avoid neutralization step due to the high solubility of this organic acid in water. As a result, the yields of isolated products have increased and reaction wastes reduced (Table 1). It should be noted that detrifluoroacetylation products were not observed in the reaction mixtures under such conditions (according to GC–MS analysis). The developed synthesis is reproducible and scalable to allow the target compounds to be easily prepared in gram quantities (up to 5 g of compounds at one synthesis run).

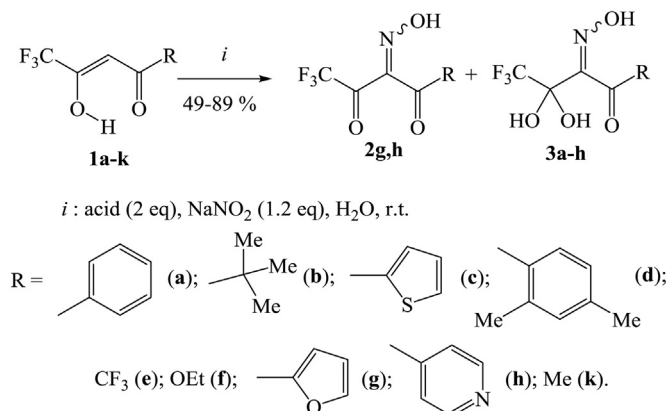
The NMR spectra of obtained compounds confirmed that these products exist predominantly as 4,4,4-trifluoro-3,3-dihydroxy-2-(hydroxyimino)butan-1-ones (**3a–h**). A characteristic feature of their  $^1\text{H}$  NMR spectra ( $\text{DMSO}-d_6$ ) is the appearance of the 2 singlets at  $\delta$  11.70–12.08 and 6.4–7.78 ppm for  $\text{NOH}$  and  $\text{CF}_3\text{C}(\text{OH})_2$  protons, respectively. In the  $^{19}\text{F}$  NMR spectra of **3a–h** the signal of  $\text{CF}_3$  group attached to the  $\text{sp}^3$ -hybridized carbon atom is exhibited as the singlet at  $\delta_{\text{F}}$  from  $-82.7$  to  $-81.7$  ppm. In the  $^{13}\text{C}$  NMR spectra of **3a–h** the  $\text{CF}_3$ -C was identified by spin-spin coupling constant  $^2 J_{\text{CF}} \sim 37$  Hz. This quartet is appeared at  $\delta_{\text{C}} \sim 92$  ppm. The signals of diketo form (**2g,h**) in NMR spectra are up-shielded in contrast to that of hydrate forms (**3g,h**). Dehydrated form **2g,h** has been easily identified by the presence of signals at  $\delta_{\text{F}}$  from  $-71.6$  to  $-71.5$  ppm in the  $^{19}\text{F}$  NMR spectra.

Next, we focused on the preparation of acyl cyanides **4** from obtained hydroxyimino derivatives **3**. We found that the reaction of compounds **3a–h** with acetic anhydride in  $\text{CHCl}_3$  under reflux gave corresponding carbonylcyanides **4a–d,f–h** in moderate yields (Table 2, Scheme 2). For compound **3e** only the mixture of decomposition products was obtained. This reaction proceeded with clear solution formation after heating of the starting suspension for 10–15 min. Further product isolation by column chromatography or distillation was required because of by-products formation derived from reactive acyl cyanides **4a–d,f–h** (checked by GC–MS analysis and  $^1\text{H}$  NMR data). We also found that the acetic acid action on compounds **3a–h** resulted in acyl cyanides **4a–d,f–h** in good yields.

It is important to note that this simple procedure represents a convenient synthetic approach to acyl nitriles that are versatile multifunctional intermediates [6]. The classical methods of acyl cyanides synthesis usually require the metal cyanides use at a high reaction temperature while the alternative ways mostly involve the several steps, including cyanosilylation, cyanohydrin formation, and oxidation [7]. However, the process described here does not require the use of hazardous chemicals or harsh reaction conditions. Furthermore, the detrifluoroacetylation occurs in the absence of common bases that are usually employed for the trifluoroacetic group elimination.

We can assume that the proposed mechanism is realized via either acylation or protonation of hydroxyimino moiety of **3** with the formation of intermediates **A** or **B** respectively (Scheme 2). It should be noted that acylation of non-fluorinated 2-hydroxyimino analogs of **2** proceeds smoothly under the same conditions [8]. In case of compounds **3**, the formation of **A** or **B** resulted in the elimination of trifluoroacetic and acetic acids to yield compounds **4**.

In conclusion, a practical approach for 2-hydroxyimino derivatives of trifluorinated 1,3-dicarbonyl compounds was elaborated. Detrifluoroacetylation of products obtained was demonstrated to be an acid-catalyzed process. Another possible



Scheme 1. The nitrozylation of trifluorinated 1,3-diketones.

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