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PREPARATION AND REACTION OF 4-METHOXYBENZYL (MPM) AND 3,4-DIMETHOXYBENZYL (DMPM) PERFLUOROIMIDATES

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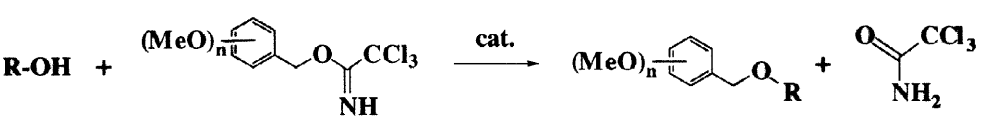
Abstract: *We have succeeded in one-pot preparation of perfluoroimidates at -78 ℃ by employing the dehydration of perfluoroamide under the "activated" dimethyl sulfoxide (DMSO) species followed by in situ nitrile trapping with alcohols. MPM and DMPM perfluoroimidates can be used to protect alcohols in place of the trichloroacetimidate with excellent chemical properties and in comparable yields.*

Benzyl-type protecting groups such as benzyl (Bn), 4-methoxybenzyl (MPM or PMB) and 3,4-dimethoxybenzyl (DMPM or DMB) groups, which are selectively deprotectable, are a versatile and frequently used protecting group in organic chemistry.[1,2] The most common way of introducing these groups is with a strong base and benzyl halide. Recently, trichloroacetimidate has found widespread use to protect hydroxy functionalities[3] and several applications were published.[4-7] The benzyl trichloroacetimidate can be prepared from the sodium alkoxide ion of benzyl alcohol and trichloroacetonitrile.[8] Substituted benzyl ethers have also been prepared this way, such as MPM (**I**),[9] DMPM (**II**)[10] and 2,6-dichlorobenzyl trichloroacetimidate,[11] and the method has also been applied for the synthesis of allyl,[3b,12] t-Bu,[13] 2-phenylisopropyl ethers.[14]

Trichloroacetimidate **I** and **II** can be used to install the corresponding protective group in the presence of a variety of other protecting groups under acidic conditions. Primary, secondary, or tertiary alcohols are simply treated with the trichloroacetimidate and 0.3 mol % triflic acid (TfOH) in ether at room temperature.[9b] However, both reagents are more reactive than their benzyl analogues and are not sufficiently stable; therefore, they are best prepared fresh. The amount of acid is also important: excessive use results in low yields and messy reactions.



I and II **n = 0, 1, 2**

In order to improve the chemical properties of these reagents, we designed and synthesized the perfluoro analogues of **I** and **II** as a more stable reagent than their trichloro analogues.[15] Brown *et al.* reported the base-catalyzed reaction of perfluoronitrile[16] with alcohols;[17] however, the handling of perfluoronitrile is quite difficult because of its volatile (cf. trifluoroacetonitrile; bp. -64 ℃) and toxic properties. Herein we describe the one-pot preparation of perfluoroimidates *via* nitrile from amide at -78 ℃.

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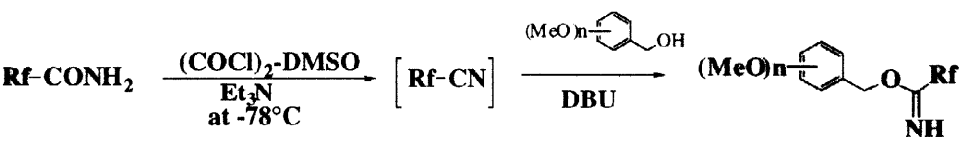
Recently, we have succeeded in the preparation of nitriles from amide by dehydration under $(COCl)_2$-DMSO and Et_3N conditions in CH_2Cl_2 at -78 °C.[18] Simple application of these reaction conditions to the preparation of trifluoroacetonitrile and the following *in situ* benzyl alcohol trapping, however, was poorly reproducible and gave only low chemical yield owing to competing alcohol oxidation to aldehyde. We were pleased to find that in the presence of 2 equiv. of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene)[19] trifluoroacetonitrile was smoothly trapped with benzyl, 4-methoxybenzyl, and 3,4-dimethoxybenzyl alcohol in good yield.[20] The obtained trifluoroacetimidates were purified by silica gel column chromatography and were stable for a month at room temperature. In order to explore this stability, combinations of perfluoroalkyl substituents [Rf = ClF_2C (**A**), F_3C (**B**), $F(CF_2)_2$ (**C**), $F(CF_2)_3$ (**D**), $H(CF_2)_2$ (**E**), $H(CF_2)_4$ (**F**), $H(CF_2)_6$ (**G**)] and $(MeO)_nC_6H_{5-n}CH_2OH$ (n = 0, 1, and 2) were then evaluated as shown in **Table I**.[21] The reaction is believed to be operationally simple and useful for the preparation of perfluoronitriles and perfluoroimidates. The overall sequence proceeded cleanly on a large scale and was reproducible.

Table I. One-Pot Synthesis of Benzyl-Type Fluorine Contained Imidates



Rf = perfluoroalkyl, n = 0,1,2

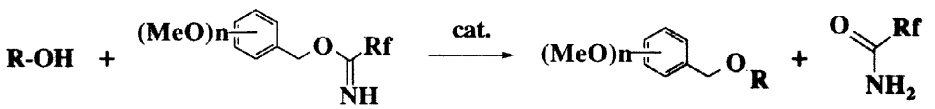
Entry	Rf	Benzyl alcohol	Yield[a,b]	Imidate
1	ClF_2C	$C_6H_5CH_2OH$	81 (40)	$\mathbf{A_0}$
2	ClF_2C	4-(MeO)$C_6H_4CH_2OH$	83	$\mathbf{A_1}$
3	ClF_2C	3,4-$(MeO)_2C_6H_3CH_2OH$	81 (36)	$\mathbf{A_2}$
4	F_3C	$C_6H_5CH_2OH$	64 (28)	$\mathbf{B_0}$
5	F_3C	4-(MeO)$C_6H_4CH_2OH$	85 (48)	$\mathbf{B_1}$
6	F_3C	3,4-$(MeO)_2C_6H_3CH_2OH$	81 (56)	$\mathbf{B_2}$
7	$F(CF_2)_2$	$C_6H_5CH_2OH$	78 (29)	$\mathbf{C_0}$
8	$F(CF_2)_2$	4-(MeO)$C_6H_4CH_2OH$	80	$\mathbf{C_1}$
9	$F(CF_2)_2$	3,4-$(MeO)_2C_6H_3CH_2OH$	82 (58)	$\mathbf{C_2}$
10	$F(CF_2)_3$	$C_6H_5CH_2OH$	77 (58)	$\mathbf{D_0}$
11	$F(CF_2)_3$	4-(MeO)$C_6H_4CH_2OH$	80	$\mathbf{D_1}$
12	$F(CF_2)_3$	3,4-$(MeO)_2C_6H_3CH_2OH$	70	$\mathbf{D_2}$
13	$H(CF_2)_2$	$C_6H_5CH_2OH$	74 (14)	$\mathbf{E_0}$
14	$H(CF_2)_4$	$C_6H_5CH_2OH$	76 (35)	$\mathbf{F_0}$
15	$H(CF_2)_6$	$C_6H_5CH_2OH$	90 (41)	$\mathbf{G_0}$

[a] Isolation yield after Kugelrohr distillation. [b] Parenthesis shows the yields in the absence of DBU.

We next focused our attention on the acid-catalyzed MPM and DMPM protection of alcohol based on the foregoing results as shown in **Table II**. Although the basicity of the nitrogen atom is reduced by electron-withdrawing perfluoro substitution on the imidate carbon, MPM protection of **1** with 4-methoxybenzyl

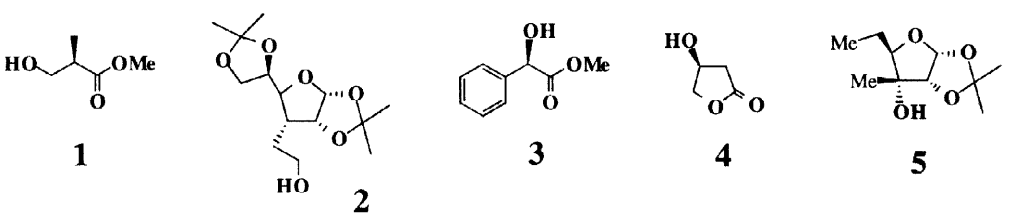
trifluoroacetimidate ($\mathbf{B_1}$) proceeded the same as with the trichloro analogue in the presence of PPTS (pyridinium p-toluenesulfonate, 13 mol %) to provide the expected MPM ether in good yields (entries 1 and 2). By using 0.3 mol % of TfOH as a catalyst in Et_2O, reaction for primary (**1**), secondary (**3**), and tertiary alcohol (**5**) proceeded within 10 min in 88%, 74%, and 70% yield, respectively (entries 3-5). The 3,4-dimethoxybenzyl (DMPM) trifluoroacetimidate ($\mathbf{B_2}$) was much more reactive than $\mathbf{B_1}$. The DMPM protection of **1** with $\mathbf{B_2}$ and PPTS (11 mol %) rapidly proceeded to completion within 60 min and 92 % yield of DMPM ether was obtained (entries 1, 2 vs. 6). Perfluoroalkyl imidates [Rf = $F(CF_2)_2$ ($\mathbf{C_2}$), $F(CF_2)_3$ ($\mathbf{D_2}$)] were also reactive for DMPM protection (entries 7-9). For the protection of secondary alcohol (**3** and **4**) with $\mathbf{B_2}$, CSA (10-camphorsulphonic acid) was an effective catalyst, giving 80% and 56% yield of products, respectively (entries 12, and 13). Unfortunately, when the reaction was performed for tertiary alcohol (**5**) by using CSA or TfOH as a catalyst, no successful results were observed (entries 14, 15).

Table II. Acid-Catalyzed 4-Methoxybenzyl (MPM) and 3,4-Dimethoxybenzyl (DMPM) Protection of Alcohol with MPM and DMPM Perfluoroacetimidates



Entry	Imidate, equiv.	Alcohol	Acid , mol %	Solvent	Time	Yield, %[a]
1	**I**, 1.3	**1**	PPTS, 13	CH_2Cl_2	24 h	88
2	$\mathbf{B_1}$, 1.3	**1**	PPTS, 13	CH_2Cl_2	24 h	80
3	$\mathbf{B_1}$, 1.3	**1**	TfOH, 0.3	Et_2O	5 min	88
4	$\mathbf{B_1}$, 1.9	**3**	TfOH, 0.3	Et_2O	10 min	74
5	$\mathbf{B_1}$, 2.5	**5**	TfOH, 0.2	Et_2O	10 min	70
6	$\mathbf{B_2}$, 1.1	**1**	PPTS, 11	CH_2Cl_2	1 h	92
7	$\mathbf{C_2}$, 1.1	**1**	PPTS, 11	CH_2Cl_2	1 h	88
8	$\mathbf{C_2}$, 2.0	**1**	PPTS, 50	CH_2Cl_2	1 h	98
9	$\mathbf{D_2}$, 2.0	**1**	PPTS, 50	CH_2Cl_2	1 h	95
10	$\mathbf{B_2}$, 1.3	**2**	PPTS, 12	CH_2Cl_2	16 h	69 (22)[b]
11	$\mathbf{B_2}$, 2.6	**2**	PPTS, 12	CH_2Cl_2	19 h	92
12	$\mathbf{B_2}$, 2.2	**3**	CSA, 15	CH_2Cl_2	5 h	80
13	$\mathbf{B_2}$, 1.5	**4**	CSA, 0.5	CH_2Cl_2	6 h	56
14	$\mathbf{B_2}$, 1.3	**5**	CSA, 4	CH_2Cl_2	13 h	-[c]
15	$\mathbf{B_2}$, 1.3	**5**	TfOH, 0.3	Et_2O	5 min	-[d]

[a] Isolation yield after chromatographic purification. [b] Parenthesis shows the recovery yield of the starting material. [c] No reaction. [d] Very rapid decomposition of **D**.



In summary, we have demonstrated that MPM and DMPM trifluoroacetimidates can serve as stable protecting reagents for hydroxy functions. Current investigations are focused on the synthesis and reactivity of the sugar analogue for coupling reagents in carbohydrate synthesis.

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20. **A typical procedure:** Preparation of DMPM trifluoroacetimidate (**B_2**. Table I, entry 6). In a flame-dried 300 mL 3-necked round-bottom flask equipped with a stirring bar, a thermometer, a septum and a nitrogen inlet were introduced trifluoroacetamide (1.80 g, 16 mmol), DMSO (3.41 mL, 48 mmol) and CH_2Cl_2 (20 mL). This solution was cooled down to -75 °C (internal) and $(COCl)_2$ (1.31 mL, 15 mmol) and Et_3N (5.3 mL, 38 mmol) were slowly added at intervals of ten minutes. No rise in temperature was observed during this process. After stirring for 30 min at -78 °C; DBU (1.5 mL, 10 mmol) and 3,4-dimethoxybenzyl alcohol (0.84 g, 5 mmol) were added slowly *via* syringe. The reaction mixture was stirred for 15 min at -78 °C, the mixture was allowed to reach room temperature over 10 h. The reaction mixture was quenched by addition of water (30 mL), the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic phases were washed with brine (100 mL), dried (Na_2SO_4), then filtered. Concentration and following purification by silica gel column chromatography (hexane/EtOAc, 5/1) and Kugelrohr distillation (bp 120-125 °C/ 0.3 mmHg) afforded the 1.07 g (81 %) of DMPM trifluoroacetimidate as a colorless solid (mp 73.0-74.0 °C) which can be stored for up to a month at room temperature.
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