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A Convenient Synthesis of α-Trifluoromethylated and α-Perfluoroalkylated Acyloins from α-Hydroxy Acids

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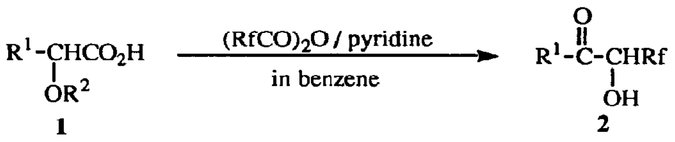
Abstract: A novel transformation of α-hydroxy acids to α-trifluoromethylated and α-perfluoroalkylated acyloins was efficiently realized by utilizing trifluoroacetic or perfluoroalkylcarboxylic anhydrides in the presence of pyridine, in which probable intermediates were meso-ionic 1,3-dioxolium-4-olates.

α-Hydroxy ketones or acyloins are very useful synthons for a variety of organic synthesis,[1] while their fluorine-containing analogues, e.g. α-trifluoromethylated acyloins have been recently reported by us[2] and others[3] as promising building blocks for trifluoromethylated compounds.[4] However, these methods result in a mixture with other products or need too many steps to be efficient in a building block strategy. Herein we report a more efficient and straitforward method for preparing α-trifluoromethylated and α-perfluoroalkylated acyloins 2 based on the reactivity of α-hydroxy acids 1 with trifluoroacetic(TFAA) or perfluorocarboxylic(PFCA) anhydrides (Scheme 1).



R^1=Ph, $PhCH_2$, $CH_3(CH_2)_5$; R^2=H, COMe, COPh; Rf=CF_3, C_2F_5, C_3F_7

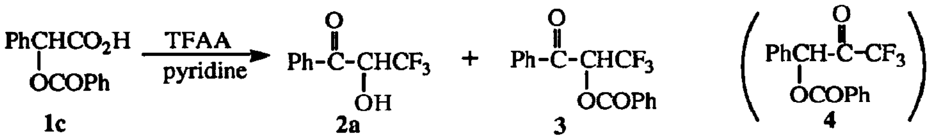
Scheme 1

We found that, upon treatment of a variety of α-hydroxy acids 1 with TFAA in the presence of pyridine, a clean reaction occurred, leading to the corresponding α-trifluoromethylated acyloins 2 in good yields (Table 1).[5] Pyridine was essential and the absence of base lowered the yield (**2a**: 5%). A high temperature (80 °C) was needed to obtain a high yield of 2, the room temperature reducing the yield (**2a**: 9 %). Pentafluoropropionic and heptafluorobutyric anhydride reacted readily with **1a** to give α-perfluoroalkylated acyloins **2b** and **2c** in good yields, respectively (Table 1, runs 5 and 6).

Table 1. Transformation of α-Hydroxy Acids **1** to α-Perfluoroalkylated Acyloins **2**.

	Starting Materials			Products			
Run	**1**	R^1	R^2	Compounds	R^1	Rf	Yield (%)[a]
1	**a**	Ph	H	**2a**	Ph	CF_3	87
2	**b**	Ph	COMe	**2a**	Ph	CF_3	88
3	**c**	Ph	COPh	**2a**	Ph	CF_3	41[b]
4	**d**	Ph	Me	--[c]	--	--	--
5[d]	**a**	Ph	H	**2b**	Ph	C_2F_5	84
6[e]	**a**	Ph	H	**2c**	Ph	C_3F_7	66
7	**e**	$PhCH_2$	H	**2d**	$PhCH_2$	CF_3	71
8	**f**	n-C_6H_{13}	H	**2e**	n-C_6H_{13}	CF_3	42

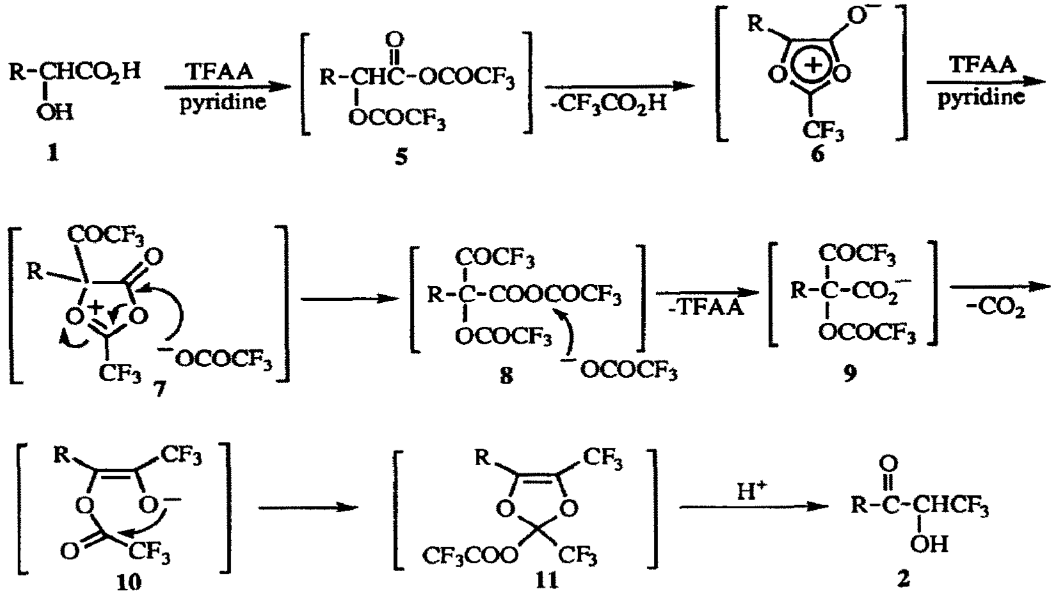
a) Isolated yields of pure products. Satisfactory spectral and analytical (combustion and/or high resolution mass) data were obtained for all products. b) Plus 42% of **3**. c) Methyl benzoate was isolated in 41% yield.[6] d) Pentafluoropropionic anhydride was used. e) Heptafluorobutyric anhydride was used.



Scheme 2

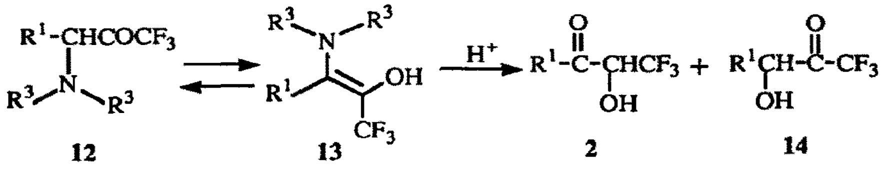
Although precise mechanistic details need yet to be established, the reaction appears to proceed *via* meso-ionic 1,3-dioxolium-4-olates **6**[7] in a similar mechanism described in the case of the Dakin-West reaction of N-alkyl-N-acyl-α-amino acids (Scheme 3).[2, 8] This speculation has been drawn from the following facts: (1) Both O-methylmandelic acid **1d** and atrolactic acid failed to give the corresponding trifluoromethyl ketones. Because these compounds can not form the meso-ionic 1,3-dioxolium-4-olates **6**. (2) O-Bezoylmandelic acids **1c** gave **2a** and 2-benzoyloxy-1-phenyl-3,3,3-trifluoro-1-propanone **3** (Scheme 2). Worth noting here is formation of none of the regioisomers 4.

Begue and co-workers describe that hydrolysis of α-amino trifluoromethylated ketones **12** results in a mixture of α-hydroxy ketones **2** and **14** (Scheme 4).[3c] This is intriguing to us, compared with our results



Scheme 3

that the single isomer of α-hydroxy ketones 2 is isolated. The calculation indicates that 2 is more thermodynamically stable than 14, and consists with our results.[9]



Scheme 4

In spite of the extensive studies of the preparation of trifluoromethyl ketones,[10] it has not been reported a reaction of simple carboxylic acids with TFAA to yield the corresponding trifluoromethyl ketones.[11]

In summary, this work describes the reaction of α-hydroxy acids and TFAA or PFCA, which has great practical prospect because of the ready availability of starting materials and reagents and ease of manipulation. Our method makes this class of compounds readily accessible for further study as building blocks for the synthesis of fluorine-containing compounds. Synthetic applications of these synthons and further mechanistic studies are now in progress.

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5. In a typical experiment, TFAA (1.2 ml, 8 mmol) was added to a stirred solution of **1a** (304 mg, 2 mmol) and pyridine (0.97 ml, 12 mmol) in dry benzene (7 ml) at room temperature under Ar atmosphere and the mixture was refluxed for 3 h. Then, 5% HCl (5 ml) was added to the mixture and the solution was stirred at 60 °C for 10 min. After usual workup, the crude product was purified by column chromatography on silica gel eluting with EtOAc-hexane (1 : 4) to give **2a** (355 mg, 87% yield), mp. 84-86 °C (lit.[3a] mp. 87 °C).
6. The unexpected formation of methyl benzoate is interesting in synthetic and mechanistic aspects and the studies are now in progress.
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9. The geometries for the acyloins (**2** and **14**, R^1=CH_3) were estimated by the full geometry optimization in the PM3 method (Stewart, J. J. P. MOPAC QCPE #549) in order to determine the more stable form. The heats of formation of **2** and **14** are -245.34583 and -240.87704 kcal mol^{-1}, respectively.
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11. Recently, it is reported that trifluoromethyl ketones are obtained from carboxylic acid chlorides by the reaction with pyridine and TFAA, in which the intermediate ketenes undergo the trifluoroacetylation. However, the reaction has failed with *secondary* acid chlorides. In one variant the sodium salt of the acid was converted to the corresponding trifluoromethyl ketone: see Boivin, J.; Kaim. L. E.; Zard, S. Z. *Tetrahedron Lett.* **1992**, 33, 1285.

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