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A convenient access to (*F*-alkyl)alkanals

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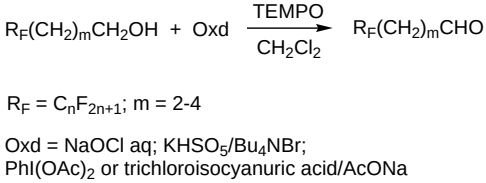
Abstract—Aldehydes $R_F(CH_2)_mCHO$ ($R_F = n\text{-}C_nF_{2n+1}$) have been prepared in good yields by oxidation of the corresponding alcohols using inexpensive and safe oxidants such as phenyliodine (III) diacetate and trichloroisocyanuric acid in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxyl free-radical (TEMPO) as a catalyst.

The synthesis of compounds containing polyfluoroalkyl substituents has attracted continuous attention from chemists due to their manifold potential applications, as diverse as active matrix liquid crystal displays and pharmaceuticals.[1,2] More recently, new strategies for recoverable catalysts and reagents based on the orthogonality of purposely designed perfluoroalkyl substituted compounds and standard organic solvents and catalysts have been demonstrated.[3] This requires the ready availability of perfluoroalkylated starting materials which can be further elaborated.

(*F*-Alkyl)alkanals $R_F(CH_2)_mCHO$ are versatile starting materials in the synthesis of several families of perfluoroalkylated compounds such as aromatic and non-aromatic heterocycles,[4,5] chiral enantiopure alcohols,[6] and aliphatic amines.[7] Therefore, there is ongoing interest in the development of convenient and effective synthetic routes to these (*F*-alkyl) building-blocks, but most procedures described so far are either low-yielding or experimentally complicated.[8] Others require special equipment and the handling of toxic materials as in the case of the hydroformylation of $R_FCH{=}CH_2$.[9,10] A few methods give good results but are limited to the synthesis of a particular product, for instance R_FCH_2CHO.[11] Two independent groups recently reported the synthesis of $R_F(CH_2)_mCHO$ by direct oxidation of the corresponding (*F*-alkyl)alkanols which are either commercially available or easily synthesised according to established procedures.[12,7] Among the stoichiometric oxidants tested, 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one (Dess–Martin periodinane, DMP)[13] gave the best results, especially when the desired aldehydes are liable to side-reactions during the work-up. Other oxidants (pyridinium chlorochromate and DMSO/$(COCl)_2$) are less appealing in view of the nature of the byproducts generated during the reaction and of the required working conditions. Despite its merits, even DMP can suffer from some drawbacks. Indeed, it is known that the behaviour of this sensitive oxidant can be capricious and that the quality of DMP batches prepared according to published procedures can be inconsistent, unless very strict methodologies are followed.[14] Although DMP has been recently made commercially available, its cost is much higher than that of other oxidants suitable for multigrams-scale reactions. We report herein a convenient approach to the selective oxidation of (*F*-alkyl)alkanols, based on the use of safe and inexpensive stoichiometric reagents in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxyl free-radical (TEMPO) as a catalyst (Scheme 1).[15]

Several oxidants were screened using (*F*-octyl)propan-1-ol **1** as a model substrate. Reactions were carried out on a millimolar scale and followed by GC/MS and ^1H NMR analyses. At first, biphasic water/organic systems (which are commonly used in TEMPO-catalysed reactions)[16] were tested, but this option is not recommendable for the oxidation of (*F*-alkyl)alkanols since



Scheme 1. Selective oxidation of (*F*-alkyl)alkanols $R_F(CH_2)_mCH_2OH$.

Keywords: oxidation; hypervalent iodine; TEMPO; perfluoroalkyl compounds.

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Table 1. Oxidation of (*F*-octyl)propan-1-ol **1** to aldehyde **2** with iodobenzene diacetate/TEMPO

Entry	TEMPO (mol%)	Time (min)	Conversion[a] (%)	Isolated yield (%)
1	1	120	15	–
2	5	120	23	–
3	10	60	100	62[b]
4	10	60	100	86[c]

[a] GC/MS and ^{1}H NMR of the crude mixture.
[b] Column chromatography (silica gel, petroleum ether/Et_2O 4/1).
[c] Selective extraction with *n*-perfluorooctane (see text).

sluggish reactions were generally observed, as in the case of aqueous NaOCl and $KHSO_5$. Moreover, in addition to (*F*-octyl)propanal **2** which is soluble in most organic solvents and perfluorocarbons, reactions yielded variable amounts of a colourless insoluble solid, later identified as the hydrate of **2** on the basis of the elemental analysis. More reproducible results were obtained using organic oxidants, in particular iodobenzene diacetate[17] and trichloroisocyanuric acid[18] which gave complete and rapid conversion of the starting alcohol at 20°C in the presence of 0.1 and 0.01 molar equiv. of TEMPO, respectively, with complete selectivity for the aldehyde as evaluated by GC/MS. Small amounts of (*F*-octyl)propanoic acid **3** (5–15%) were detected in the crude reaction mixture when the oxidation of **1** was run on a larger scale with trichloroisocyanuric acid. This inconvenience can be avoided if the reaction is carried out at 0°C in the presence of AcONa as a base.[19] However, since the use of iodobenzene diacetate afforded **2** as the only fluorinated product, this oxidant was chosen for the optimisation of the reaction conditions.

Addition of less than 0.1 molar equiv. of TEMPO resulted in incomplete conversion of **1** (Table 1, entries 1 and 2) even at long reaction times. Portionwise addition of the catalyst and lower reaction temperatures did not change the outcome of the reaction. Recovery of the sensitive (*F*-octyl)propanal **2** from reaction mixtures by means of distillation under reduced pressure has been reported,[7,12] but this procedure can lead to severe losses of product unless strictly controlled experimental conditions are followed.[9] Column chromatography on silica gel and selective extraction with *n*-perfluorooctane were tested as more flexible alternatives to distillation for laboratory-scale reactions (entries 3 and 4). Both methods afforded **2** in good yields, but selective extraction was preferred because of its ease, rapidity and low solvent consumption.

In a typical experiment, alcohol **1** (4.78 g, 10 mmol) was dissolved in CH_2Cl_2 (10 ml). The flask was dipped in a water bath at 20°C and TEMPO (1 mmol, 156 mg) was added under stirring. Iodobenzene diacetate (3.54 g, 11 mmol) was added to the solution over 5 minutes and stirring was maintained until GC/MS analysis showed that the alcohol was consumed (60 min). The solution was transferred into a separatory funnel, the flask was washed with CH_2Cl_2 (10 ml) and the combined liquid layers were washed with a saturated aqueous solution of $Na_2S_2O_3$ (3 ml), 5% aqueous $NaHCO_3$ (3 ml) and brine (3 ml). The organic phase was dried (Na_2SO_4) and the solvent was eliminated by evaporation under a pressure of 200 mmHg at 30°C. CH_3CN (5 ml) and *n*-perfluorooctane (10 ml) were added to the liquid biphasic residue. After shaking, the upper organic layer was separated and washed with *n*-perfluorooctane (5 ml). The combined fluorocarbon layers were washed with CH_3CN (2 ml) and evaporated under a pressure of 50 mmHg at 40°C. Aldehyde **2** was obtained as a pale yellow oil (4.09 g, 86%) showing analytical data in full agreement to those reported in the literature.[7]

This procedure applied to the oxidation of a series of (*F*-alkyl)alkanols $R_F(CH_2)_mCH_2OH$ with $R_F = C_6F_{13}$, C_8F_{17}, $C_{10}F_{21}$ and $m = 2$, 3 and 4 (Table 2) afforded the corresponding aldehydes in good isolated yields, with the exception of $C_6F_{13}(CH_2)_2CHO$ **4** (entry 1).[†] The

Table 2. Oxidation of (*F*-alkyl)alkanols with iodobenzene diacetate/TEMPO[a]

Entry	Alcohol	Time (min)	Isolated yield (%)
1	$C_6F_{13}(CH_2)_2CH_2OH$[b]	60	–
2	$C_6F_{13}(CH_2)_3CH_2OH$[c]	45	60
3	$C_8F_{17}(CH_2)_3CH_2OH$[d]	45	79
4	$C_8F_{17}(CH_2)_4CH_2OH$[e]	60	73
5	$C_{10}F_{21}(CH_2)_3CH_2OH$[f,g]	60	83

[a] See the typical experimental procedure described above.
[b] See Ref. 20.
[c] See Ref. 21.
[d] See Ref. 22.
[e] See Ref. 7.
[f] See Ref. 23.
[g] Solvent = $CH_2Cl_2/CF_2ClCFCl_2$ 9:1 v/v.

[†] All the isolated aldehydes gave satisfactory analytical data, in agreement with those reported in the literature for known compounds. $C_{10}F_{21}(CH_2)_3CHO$: mp 89°C; ^{1}H NMR ($CDCl_3$): δ 1.90–1.99 (m, 2H, $CH_2CH_2R_F$), 2.04–2.22 (m, 2H, $CH_2CH_2R_F$), 2.59 (t, $^3J_{HH} = 7$ Hz, 2H, O=CHCH_2), 9.79 (br s, 1H, O=CHCH$_2$); ^{13}C NMR ($CDCl_3$): δ 19.9, 30.0 (t, $^2J_{CF} = 21$ Hz), 42.7, 200.1; ^{19}F NMR ($CDCl_3$): δ −81.2 (t, $^3J_{FF} = 10$ Hz, 3F, CF_3), −115.0 (t, br s, 2F), −122.2 (br s, 10F), −123.1 (br s, 2F), −123.9 (br s, 2F), −126.5 (br s, 2F).

corresponding alcohol was completely converted to **4** in 30 minutes, as evaluated by GC/MS analysis of the reaction mixture, but the aldehyde is too volatile to be isolated according to the present method. In many instances, reaction mixtures containing (*F*-alkyl)-alkanals are used as such for further synthetic steps.[4] Accordingly, addition of 2 molar equiv. of benzylamine and an excess of $Na(AcO)_3BH$ to the solution containing **4** afforded $(C_6F_{13}(CH_2)_3)(C_6H_5)NH$ **5** in 55% yield after purification by column chromatography.

Oxidation of (*F*-alkyl)alkanols $R_FCH_2CH_2OH$ has been reported to be rather troublesome, with massive formation of unsaturated aldehydes that can be avoided using the hypervalent iodine (V) DMP oxidant and weakly alkaline conditions during the purification step.[12] When the oxidation of $C_8F_{17}CH_2CH_2OH$ **6** with iodobenzene diacetate/TEMPO was attempted, elimination was not observed, but conversions were consistently low, never exceeding the introduced amount of nitroxyl free radical (10%). In contrast to this finding, the oxidising system trichloroisocyanuric acid/AcONa/TEMPO (0.4/1.1/0.02 molar equiv.) afforded complete conversion of **6** with the formation of $C_8F_{17}CH_2CHO$ **7** together with traces of $C_7F_{15}CF{=}CHCHO$ **8**. The crude product (purity>95% by GC/MS) was obtained in 87% yield as a white solid (NMR data in agreement to those reported in the literature),[11] only partly soluble in halogenated and fluorinated solvents. Our attempts at further purifying it by distillation under reduced pressure as previously described,[11] were not satisfactory since we observed partial decomposition of the white solid upon heating. We are currently trying to circumvent this problem in order to extend the scope of the TEMPO catalysed oxidation to the $R_FCH_2CH_2OH$ series.

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