

Uncatalyzed Meerwein–Ponndorf–Verley reduction of trifluoromethyl carbonyl compounds by high-temperature secondary alcohols

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Abstract

Noncatalytic Meerwein–Ponndorf–Verley (MPV) reduction of hexafluoroacetone and methyl ester of trifluoropyruvic acid into hexafluoroisopropanol (HFIP) and trifluorolactic esters, respectively can be achieved by heating with secondary alcohols at 210–250 °C without any catalyst.

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1. Introduction

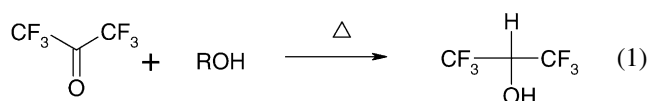
The Meerwein–Ponndorf–Verley (MPV) reduction of carbonyl compounds is one of the important reactions in synthetic organic chemistry. Usually a stoichiometric amounts of metal alkoxides are required to obtain good yields of desired alcohols [1]. Several attempts have been recently made to prepare homogeneous [2–4] and heterogeneous [5–7] catalysts for the improved MPV reduction of carbonyl substrates.

In a recent publication it was shown that aldehydes and ketones can be reduced by alcohols at elevated temperatures without a catalyst [8]. The reaction needs a high alcohol: substrate ratio (100:1) and long reaction time (24–29 h); ketones are less active than aldehydes.

In the present work, we have investigated the MPV reduction of two trifluoromethyl carbonyl compounds, namely hexafluoroacetone (HFA) and the methyl ester of trifluoropyruvic acid (methyl trifluoropyruvate (MTP)) by high-temperature alcohols (the term “high-temperature” means that alcohols are heated above their boiling point). Both reaction products (hexafluoroisopropanol (HFIP) [9] and trifluorolactic acid [10,11], respectively) are valuable industrial and/or synthetic reagents.

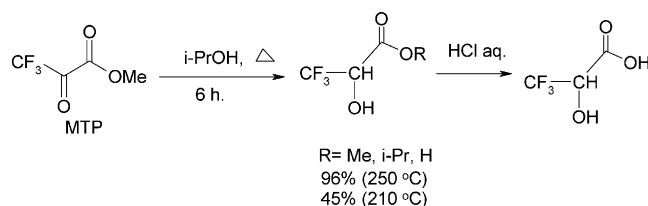
1.1. Results and discussion

We have found that hexafluoroacetone (taken as sesquihydrate, HFA·1.5 H₂O) is readily reduced to hexafluoroisopropanol (HFIP) by secondary alcohols without any catalyst at elevated temperatures (Eq. (1)).

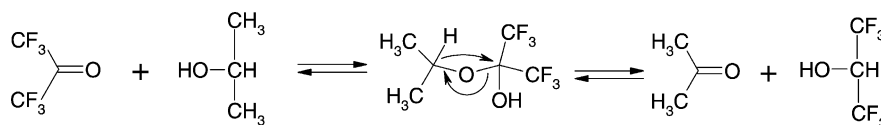


Primary alcohols appeared to be less active than secondary (entries 1–4 in Table 1); both *i*-PrOH and butanol-2 showed approximately equal activity (entries 4 and 5). Only a small reduction in yield was observed when HFA: *i*-PrOH ratio was reduced from 1:10 to 1:1.5.

The methyl ester of trifluoropyruvic acid (MTP) can also be reduced to trifluorolactic esters using the same procedure (Eq. (2)).



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Scheme 1.

Table 1
Hexafluoroacetone (HFA) reduction by high-temperature alcohols

Entry	R	HFA:ROH (mol)	T (°C/6 h)	HFIP Yield (%)
1	Me	1:10	180	0
2	Me	1:10	220	30
3	Et	1:10	180	10
4	<i>i</i> -Pr	1:10	180	43
5	2-Bu	1:10	180	42
6	<i>i</i> -Pr	1:10	200	73
7	<i>i</i> -Pr	1:10	220	86
8	<i>i</i> -Pr	1:10	240	96
9	<i>i</i> -Pr	1:1.5	220	75
10	<i>i</i> -Pr	1:1.5	240	88
11 ^a	<i>i</i> -Pr	1:1	210	65

^a Nonaqueous HFA-*i*-PrOH compound [12] was used.

A mixture of free trifluorolactic acid and its methyl and isopropyl esters is obtained as a result of transesterification; further, this mixture can be easily converted to a pure acid by hydrolysis.

Both compounds (HFA and MTP) are more active in this reaction than the non-fluorinated ketones and aldehydes investigated by Bagnell and Strauss [8] and substantially shorter reaction times and smaller substrate: alcohol ratios are required. This may be due to a greater 'oxidative' potential of fluorinated carbonyl compounds compared with non-fluorinated analogues.

The reaction mechanism undoubtedly includes formation of an alcohol-HFA compound [12] and a reversible hydride transfer, which is accelerated by high-temperature and hence does not need a catalyst (Scheme 1).

It may be concluded that heating with secondary alcohols can be a convenient method of MPV reduction of fluorinated carbonyl compounds.

2. Experimental

¹H and ¹⁹F NMR spectra were recorded on a Bruker DPX-200 spectrometer. Chemical shifts are referred to the external standards Me₄Si and CF₃COOH, respectively. Hexafluoroacetone sesquihydrate (HFA·1.5 H₂O) and the methyl ester of trifluoropyruvic acid MTP (both of 98% purity) were produced by Unisintez Ltd., Russia. Reactions were carried out in a stainless steel 40 ml autoclave equipped with a pocket for a thermocouple and a D-60 tensometric sensor for precision pressure monitoring.

2.1. Hexafluoroisopropanol

In a typical experiment, an autoclave filled with 5 ml of the mixture containing HFA·1.5 H₂O and *i*-PrOH in 1:10 mol ratio was heated in a furnace equipped with a device for automated temperature maintenance and the temperature and pressure inside the autoclave were monitored during heating. After the end of heating, the autoclave was cooled and the reaction mixture was analyzed by ¹⁹F NMR. The HFA to HFIP ratio was determined by integration thus giving the yield of the product (in a special experiment it was shown that both HFA and HFIP do not lose CF₃-groups under reaction conditions). HFIP can be isolated as a pure substance by distillation of the reaction mixture from concentrated H₂SO₄. The (bp: 56–58 °C) ¹H and ¹⁹F NMR spectra coincide with those of a commercial sample.

2.2. Trifluorolactic acid

A solution of 7.8 g (0.05 mol) of MTP in 10 ml of *i*-PrOH was heated at 250 °C during 6 h in an autoclave. After cooling the reaction mixture was analyzed by ¹⁹F NMR revealing three doublets (96% overall content by integration) which were attributed to CF₃CH(OH)COOR (R = H, Me and *i*-Pr). The reaction mixture was poured into 100 ml of 2 M HCl and the solution was refluxed during 6 h. The mixture was made alkaline by 5 M KOH (pH 12), extracted by CHCl₃ and Et₂O and acidified to pH 1 by concentrated HCl. The acidified solution was extracted by Et₂O (4 × 20 ml), combined extracts were dried over Na₂SO₄, all volatiles were evaporated on a rotary evaporator and the residual oil was dried by high-vacuum pumping giving 3 g (41%) of trifluorolactic acid as a waxy solid. ¹H NMR (d₇ DMF): 4.9 (quartet, ³J_{H-F} = 7.6 Hz, 1H), 8.1 (broad s, 2H). ¹⁹F NMR: 1.4 (d, ³J_{F-H} = 7.9 Hz). The ¹H NMR (CDCl₃-CD₃OD): 4.6 (quartet, 1H), 5.15 (s, 2H) [10].

Acknowledgements

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