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A mild hydrodehalogenation of fluoroalkyl halides

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ABSTRACT

A mild hydrodehalogenation reaction of fluoroalkyl halides (R_fCF_2X, X = Br, I) has been developed under weakly basic conditions, giving the corresponding hydrogenolysis products with moderate to high yields.

1. Introduction

The C–X bonds in fluoroalkyl halides (R_fCF_2X, X = Br, I) are strong and remain intact in many reactions. However, they can be cleaved under certain conditions. For example, silyl enol ethers of ketones reacted with CF_3I and Et_2Zn in the presence of $RhCl(PPh_3)_3$ in DME to give α-trifluoromethyl ketones in good yields [1]. Perfluoroalkyl anion reagents have been obtained by mixing C_2F_5I and n-C_4F_9I with tetrakis(dimethylamino)ethylene [2]. The radical addition of perfluoroalkyl iodides to ethyl-2-carbethoxy-2-phthalimido-pent-4-enoate can be initiated by Et_3B/O_2 at room temperature [3]. And reactions between CF_3X (X = Cl, Br, I) and tetrafluoroethylene, catalyzed by aluminum chlorofluoride, afford the corresponding compounds $CF_3CF_2CF_2X$ [4].

Hydrodehalogenation is another important method for breaking the C–X bonds of fluoroalkyl halides, and is usually catalyzed by transition metal. Nevertheless, it is not a synthetically useful reaction under these conditions [5–10]. For example, hydrodehalogenation took place in the reaction of perfluoroalkyl iodides with cyclohexene or pyrrole in the presence of catalytic amounts of reductive metals [9,10]. Complete hydrodehalogenation was achieved for the first time by Durual from the reaction of perfluoroalkyl iodides in alkaline alcohol solutions [11]. Howell modified the reaction conditions afterwards and hydrofluoroalkanes were obtained in good yields from the reaction of 1-haloperfluoroalkanes using sodium methoxide as the base [12]. However, drastic conditions such as high temperature and pressure or an excess amount of concentrated strong base were required for the complete conversion of fluoroalkyl halides [11–13]. Once started, the reaction becomes difficult to control, with the rapid build-up of pressure. This could violently rupture the reaction vessel, releasing the reaction mixture and causing personal injury [12].

During the investigation of the reaction of 1,1,2,2-tetrafluoro-2-(1,1,2,2-tetrafluoro-2-iodoethoxy)ethanesulfonamide (**1a**) under basic conditions, we made the unexpected discovery that **1a** was hydrodeiodinated. Further study revealed that the reaction can take place under mild conditions. Herein, we report the experimental details of this hydrodehalogenation.

2. Results and discussion

At first, we found that the hydrodehalogenation of **1a** took place in methanol using sodium hydroxide as the base. After acidification, 1,1,2,2-tetrafluoro-2-(1,1,2,2-tetrafluoroethoxy)ethanesulfonamide (**2a**) was obtained in 70% yield (entry 1, Table 1). Then, we used $Cl(CF_2)_4I$ as a model substrate to explore the applicability of this reaction under various conditions.

As indicated in Table 1, the reaction was performed in different alkaline solvents. Temperature played an important role in this reaction. High temperatures led to a high yield of 1-chloro-1,1,2,2,3,3,4,4-octafluorobutane (**2b**) regardless of the solvent and base used (entries 2 and 3, entries 5 and 6, entries 12 and 13). For example, at 80 °C, **2b** was formed in quantitative yield in methanol and 80% yield in DMF (entries 3 and 6). Methanol was a good solvent for the deiodination of perfluoroalkyl iodides (entries 3, 4, 6 and 14). Considering the high volatility of methanol and its similar boiling point to those of the hydrodehalogenated products,

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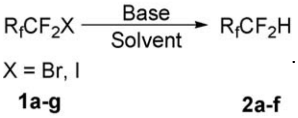
Table 1
The reaction of R_fCF_2X with base.



Entry	R_f	X	R_fCF_2X	Base (B)	Solvent	R_fCF_2X:B[a]	Temperature (*T*/°C)	Time (h)	Yield[b] (%)
1	$H_2NSO_2C_2F_4OCF_2$	I	**1a**	NaOH	CH_3OH	1:3	Reflux	3	70 (**2a**)
2	$Cl(CF_2)_3$	I	**1b**	NaOH	CH_3OH	1:3	r.t.	28	55 (**2b**)
3	$Cl(CF_2)_3$	I	**1b**	NaOH	CH_3OH	1:2	80	10	100 (**2b**)
4	$Cl(CF_2)_3$	I	**1b**	NaOH	H_2O	1:2	80	12	2 (**2b**)
5	$Cl(CF_2)_3$	I	**1b**	NaOH	DMF	1:2	r.t.	24	18 (**2b**)
6	$Cl(CF_2)_3$	I	**1b**	NaOH	DMF	1:2	80	25	80 (**2b**)
7[c]	$Cl(CF_2)_3$	I	**1b**	NaOH	DMF/H_2O	1:2	80	22	100 (**2b**)
8[d]	$Cl(CF_2)_3$	I	**1b**	NaOH	DMF/H_2O	1:2	80	22	100 (**2b**)
9[d]	$Cl(CF_2)_3$	I	**1b**	Na_2CO_3	DMF/H_2O	1:2	80	22	52 (**2b**)
10[d]	$Cl(CF_2)_3$	I	**1b**	NEt_3	DMF/H_2O	1:2	80	20	95 (**2b**)
11[d]	$Cl(CF_2)_3$	I	**1b**	DMAP	DMF/H_2O	1:2	80	18	0 (**2b**)
12	$Cl(CF_2)_3$	I	**1b**	$K_3PO_4{\cdot}3H_2O$	DMF	1:1	r.t.	20	0 (**2b**)
13	$Cl(CF_2)_3$	I	**1b**	$K_3PO_4{\cdot}3H_2O$	DMF	1:1	80	16	65 (**2b**)
14	$Cl(CF_2)_3$	I	**1b**	$K_3PO_4{\cdot}3H_2O$	DMF	1:2	80	16	100 (**2b**)
15	$H_2NSO_2C_2F_4OCF_2$	I	**1a**	$K_3PO_4{\cdot}3H_2O$	DMF	1:3	80	17	100 (**2a**)
16	$ClCF_2$	I	**1c**	$K_3PO_4{\cdot}3H_2O$	DMF	1:2	80	38	11 (**2c**)
17	$CF_3(CF_2)_4$	I	**1d**	$K_3PO_4{\cdot}3H_2O$	DMF	1:1.6	80	15	100 (**2d**)
18	$C_6H_5OCF_2$	Br	**1e**	$K_3PO_4{\cdot}3H_2O$	DMF	1:2	80	90	9 (**2e**)
19	$C_3N_2H_3CF_2$[e]	Br	**1f**	$K_3PO_4{\cdot}3H_2O$	DMF	1:2	80	77	30 (**2f**)
20	$Cl(CF_2)_3$	Br	**1g**	$K_3PO_4{\cdot}3H_2O$	DMF	1:2	80	23	90 (**2b**)
21[f]	$Cl(CF_2)_3$	I	**1b**	$K_3PO_4{\cdot}3H_2O$	DMF	1:2	80	21	23 (**2b**)
22	$Cl(CF_2)_3$	I	**1b**	NaOH	CH_3OH	1:1	r.t.	21	45 (**2b**)
23[c]	$Cl(CF_2)_3$	I	**1b**	NaOH	CH_3OH	1:1	r.t.	21	0 (**2b**)

[a] Molar ratio.
[b] Determined by ^{19}F NMR.
[c] DMF:H_2O = 10:1 (volume ratio), H_2O:NaOH = 28:1 (molar ratio).
[d] DMF:H_2O = 100:1 (volume ratio), H_2O:NaOH = 3:1 (molar ratio).
[e] 1-(2-Bromo-1,1,2,2-tetrafluoroethyl)-1H-imidazole.
[f] p-Dinitrobenzene was added and the molar ratio of p-dinitrobenzene to **1b** was 1:5.

solvents with higher boiling points were chosen as the substitutes (entries 4 and 6). In water, almost no **2b** was generated at 80 °C after 12 h (entry 4). When the reactions were conducted in DMF, hydrodehalogenation was found to proceed smoothly (entries 6–8 and 14), indicating that DMF is a good substitute for methanol. In addition, the reaction was improved when carried out in a mixture of DMF and water (entries 6–8). Compound **1b** was completely converted into the dehalogenated product in the presence of a small amount of water (entries 7 and 8).

The hydrodehalogenation was also influenced by the base used. Using NaOH as the base, **2b** could be formed in quantitative yield in DMF (entries 7 and 8). Similar results were achieved when NaOH was replaced by NEt_3 (entry 10). When Na_2CO_3 was selected, only a 52% yield of **2b** was obtained (entry 9). These results indicated that increasing the strength of the base used in the reaction would improve the rate of the hydrodeiodination of perfluoroalkyl iodides. However, when DMAP was employed as the base and the reaction mixture was heated at 80 °C for 18 h, none of the product **2b** was formed (entry 11), suggesting that DMAP is not a good reagent for the reduction of perfluoroalkyl iodides. Although the deiodination of **1b** worked well in DMF in the presence of NaOH, there is the possibility that DMF might be hydrolyzed under these strongly basic conditions [14]. If this is the case, it would make it difficult to separate the reaction products from the hydrolyzed products of DMF. Therefore, $K_3PO_4{\cdot}3H_2O$ was selected as a substitute for NaOH. It was found that **2b** was obtained in quantitative yield when the reaction was carried out in DMF at 80 °C for 16 h while using $K_3PO_4{\cdot}3H_2O$ as the base (entry 14). The amount of $K_3PO_4{\cdot}3H_2O$ used also had some influence on the reaction. Compound **2b** was formed only in 65% yield under these conditions when equimolar amount of **1b** and $K_3PO_4{\cdot}3H_2O$ were used (entry 13). Increasing the ratio of $K_3PO_4{\cdot}3H_2O$ to **1b** resulted in complete conversion (entry 14). It should be noted that all the reactions proceeded very well under these mild conditions, without any incidents in which the reaction flask was ruptured. Compared with the previous reports, these could be considered to be much milder reaction conditions in view of the weak basicity of K_3PO_4 and the effectiveness of the hydrodehalogenation [11,12].

Having found that the use of $K_3PO_4{\cdot}3H_2O$ as the base and DMF as solvent was optimal for the substrate **1b**, the scope of the reaction was then studied with other fluoroalkyl halides. As shown in Table 1, the hydrodeiodination of **1a** proceeded very well in the $K_3PO_4{\cdot}3H_2O$/DMF system. Compound **2a** was formed in a satisfactory yield when the reaction was run at 80 °C for 17 h (entry 15). In the case of **1d**, the hydrodehalogenation product of 1H-perfluorohexane (**2d**) was formed in quantitative yield even when a lower molar ratio of $K_3PO_4{\cdot}3H_2O$ and a shorter reaction time was used (entry 17). However, the reaction of **1c** led to the formation of 1-chloro-1,1,2,2-tetrafluoroethane (**2c**) in a yield of only 11% even when the reaction was run at 80 °C for 38 h (entry 16). These results suggest that fluoroalkyl iodides with long alkyl chains are easier to reduce under these reaction conditions. This method was also effective for the hydrodehalogenation of fluoroalkyl bromides. Thus, similar results were obtained for the hydrodebromination of **1e**–**g** (entries 18–20), in which fluoroalkyl bromides with longer alkyl chains again underwent more rapid debromination.

To understand the mechanism of this hydrodehalogenation, various inhibition experiments were carried out. Addition of 20 mol% of the electron transfer scavenger p-dinitrobenzene to the reaction of **1b** in the $K_3PO_4{\cdot}3H_2O$/DMF system decreased the yield of **2b** from 100% (entry 14) to 23% (entry 21). Furthermore, reaction of **1b** in the NaOH/CH_3OH system was completely inhibited by p-dinitrobenzene (entries 22 and 23). On the basis of these experiments, it appears that the radical $R_fCF_2^{\cdot}$ might be involved in these reactions, indicating a single electron transfer mechanism for this hydrodehalogenation initiated by base [12,15,16].

3. Conclusion

In summary, we have shown that the hydrodehalogenation of perfluoroalkyl halides proceeds smoothly in DMF in the presence of $K_3PO_4·3H_2O$. This offers a simple and efficient method for the conversion of perfluoroalkyl halides into the corresponding hydrogenolysis compounds. When bases are used in the reactions of fluoroalkyl bromides or iodides, the potential hydrodehalogenation reactions should be considered.

4. Experimental

4.1. General

NMR spectra were recorded in dueterated chloroform, unless otherwise stated, on Mercury 300 at 300 MHz (^1H NMR) and 282 MHz (^{19}F NMR). Chemical shifts were reported in ppm relative to TMS and $CFCl_3$ (positive for downfield shifts) as external standards.

*4.2. Preparation of 1,1,2,2-tetrafluoro-2-(1,1,2,2-tetrafluoroethoxy)ethanesulfonamide (**2a**)*

1a (1.01 g, 2.38 mmol) and $K_3PO_4·3H_2O$ (1.88 g, 6.58 mmol) were placed in a 25 ml round-bottomed flask equipped with a magnetic stirrer. DMF (10 ml) was added. The mixture was heated to 80 °C for 17 h, then cooled and poured into 50% sulfuric acid solution for acidification till pH < 1. The acidified mixture was extracted with ethyl ether (80 ml), washed with water (3× 30 ml) and dried over anhydrous Na_2SO_4. The crude product was purified by column chromatography to give 0.580 g of pure **2a** (82%). ^1H NMR (CD_3COCD_3) δ 6.60 (tt, J = 52 Hz, J = 3.2 Hz, 1H), 8.07 (s, 2H), ^{19}F NMR (CD_3COCD_3) δ −76.8 (m, 2F), −84.1 (m, 2F), −112.9 (s, 2F), −134.3 (dt, J = 52 Hz, J = 4.2 Hz, 2F).

*4.3. Typical procedures for the preparation of **2b–d***

1b (2.19 g, 6.04 mmol) and $K_3PO_4·3H_2O$ (3.46 g, 12.1 mmol) were placed in a sealed tube equipped with a magnetic stir bar. DMF (15 ml) was added. The sealed tube was kept at 80 °C for 16 h. On completion **2b** was distilled out carefully and collected in a trap cooled to −196 °C. After thawing, 1.21 g of pure **2b** was obtained (85%).

*4.3.1. 1-Chloro-1,1,2,2,3,3,4,4-octafluorobutane (**2b**)*

^1H NMR δ 6.04 (tt, J = 52 Hz, J = 5.0 Hz, 1H), ^{19}F NMR δ −67.6 (t, J = 11.9 Hz, 2F), −121.0 (t, J = 7.2 Hz, 2F), −128.0 (m, 2F), −136.3 (dt, J = 52 Hz, J = 6.2 Hz, 2F).

*4.3.2. 1-Chloro-1,1,2,2-tetrafluoroethane (**2c**)*

^1H NMR δ 5.86 (tt, J = 54 Hz, J = 2.3 Hz, 1H), ^{19}F NMR δ −72.4 (t, J = 7.2 Hz, 2F), −131.8 (dt, J = 53.6 Hz, J = 7.2 Hz, 2F).

*4.3.3. 1,1,1,2,2,3,3,4,4,5,5,6,6-Tridecafluorohexane (**2d**)*

^1H NMR δ 6.05 (tt, J = 52 Hz, J = 5.0 Hz, 1H), ^{19}F NMR δ −80.2 (t, J = 9.2 Hz, 3F), −122.3 (m, 2F), −122.9 (s, 2F), −125.6 (m, 2F), −128.6 (m, 2F), −136.4 (dm, J = 52 Hz, 2F).

*4.4. Typical procedure for the preparation of **2e** and **2f***

1f (0.498 g, 2.01 mmol) and $K_3PO_4·3H_2O$ (1.059 g, 3.98 mmol) were placed in a sealed tube equipped with a magnetic stir bar. DMF (15 ml) was added and the mixture was heated to 80 °C for 77 h, then cooled, extracted with ethyl ether (60 ml), washed with water (3× 20 ml) and dried over anhydrous Na_2SO_4. The crude product was purified by column chromatography to give pure **2f** in 21% yield.

*4.4.1. 1-(1,1,2,2-Tetrafluoroethyl)-1H-imidazole (**2f**)*

^1H NMR δ 7.81 (s, 1H), 7.20 (s, 1H), 7.18 (s, 1H), 6.06 (t, J = 54 Hz, 1H), ^{19}F NMR δ −96.1 (s, 2F), −135.1 (d, J = 54 Hz, 2F).

*4.4.2. 1-(1,1,2,2-Tetrafluoroethoxy)benzene (**2e**)*

^1H NMR δ 5.91 (tt, J = 53 Hz, J = 2.8 Hz 1H), 7.25 (m, 3H), 7.38 (m, 2H), ^{19}F NMR δ −88.1 (t, J = 6.2 Hz, 2F), −136.7 (dt, J = 53 Hz, J = 6.2 Hz, 2F).

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