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Mendeleev Commun., 2023, **33**, 387–389

Mendeleev Communications

Photocatalytic reduction of fluoroalkyl-substituted alcohols activated by pentafluoropyridine

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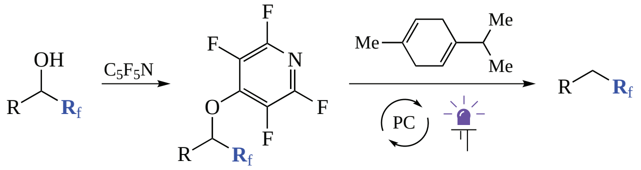
DOI: 10.1016/j.mencom.2023.04.028

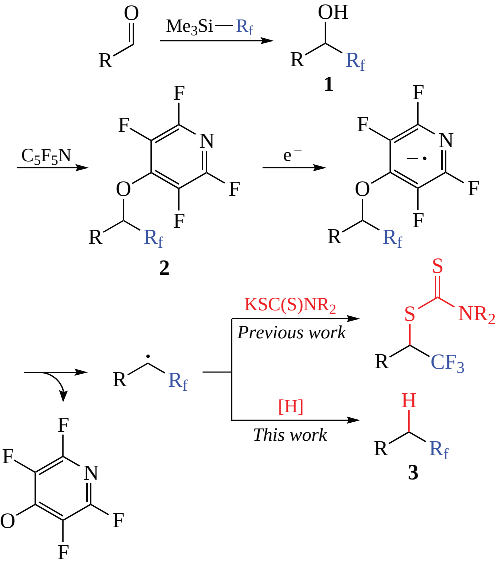
A new method for deoxygenation of fluoroalkyl-substituted alcohols involves derivatization of the hydroxy group with pentafluoropyridine followed by photoredox catalyzed reduction of the obtained hetaryl ethers using γ-terpinene as a source of hydrogen. The initial alcohols can be easily obtained by nucleophilic fluoroalkylation of the corresponding aldehydes.



Keywords: photocatalysis, radicals, deoxygenation, organofluorine compounds, alcohols, ethers.

Organofluorine compounds have received much attention in the development of pharmaceuticals and agrochemicals due to the ability of fluorine to significantly increase its biological activity.[1,2] In particular, substances containing fluoroalkyl fragment at the end of a saturated carbon chain may be needed because of the ability of fluorinated groups to modify lipophilic and conformational properties.[3,4] There are several methods for the synthesis of such compounds by deoxofluorination of carboxylic acids,[5] hydroperfluoroalkylation of terminal alkenes,[6–9] or by copper-catalyzed Csp^3–Csp^3 fluoroalkylation[10] reactions. However, these approaches have been used mostly for the introduction of the CF$_3$-group. Herein, we describe a method for the reductive radical deoxygenation of alcohols **1** resulting from nucleophilic fluoroalkylation of carbonyl compounds.[11–13]

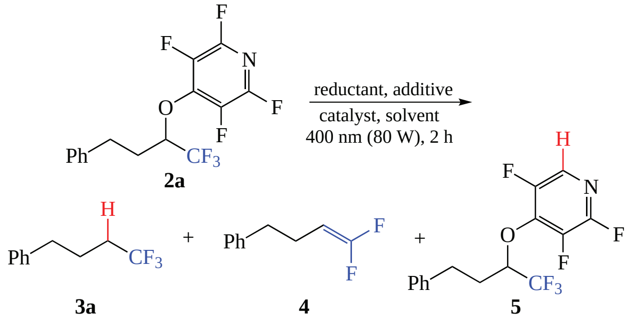
Since the discovery of the Barton–McCombie reduction of thioesters with tributyltin hydride,[14,15] several methods of radical deoxygenation and functionalization of alcohols have been developed employing various derivatizing groups such as *N*-hydroxypyridine-2-thione,[16] xanthates,[17,18] phosphites,[19] oxalates[20] and 3,5-bis(trifluoromethyl)benzoates[21] and using tris(trimethylsilyl)silane,[22–24] and hydrazine[25,26] as hydrogen donors; some of the reactions were carried out under photocatalytic conditions. Methods for the direct radical activation of free alcohols by transition metals[27] and under photocatalytic[28,29] conditions are also known.



Scheme 1

We have recently investigated the activity of tetrafluoropyridine group in reactions of photocatalytic cleavage of C–S[30–33] and C–O[34] bonds. We have shown that ethers **2** obtained from fluorinated alcohols **1** would undergo photocatalytic substitution by dithiocarbamate anion (Scheme 1). The reaction presumably goes through a single-electron activation of the substrate followed by dissociation of the C–O bond leading to stable pyridinyloxy anion and an alkyl radical. Herein we present a method for the trapping of these radicals using a readily accessible source of hydrogen atom.

Compound **2a** was selected as a model substrate and its reaction with different organic reducing agents under irradiation with 400 nm light emitting diodes was evaluated (Scheme 2). The reaction in acetonitrile with *N*,*N*-diisopropylethylamine (DIPEA) and substoichiometric amount of cyclohexanethiol (CySH) as a mediating radical quencher and 12-phenyl-12*H*-benzo[*b*]phenothiazine (BPT)[35] as a photocatalyst proceeded



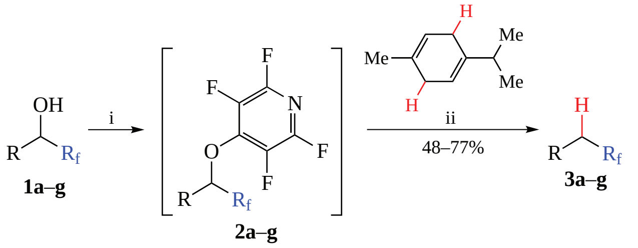
Scheme 2

Table 1 Optimization studies.

Entry	Reductant (equiv.)	Additive (equiv.)	Catalyst (mol%)	Solvent	Ratio **2a**/**3a**/**4**/**5**[a]	Yield of **3a** (%)[b]
1	DIPEA (1.5)	CySH (0.2)	BPT (3)	MeCN	0 : 74 : 21 : 5	39
2	DIPEA (1.5)	CySH (0.2)	3DPA2FBN (0.5)	MeCN	<1 : 25 : 19 : 55	n.d.[c]
3	DIPEA (1.5)	CySH (0.2)	$[Ir(dtbbpy)(ppy)_2]PF_6$ (0.25)	MeCN	13 : 50 : 16 : 21	10
4	DIPEA (1.5)	CySH (0.2)	$Ir(ppy)_3$ (0.25)	MeCN	65 : 15 : 0 : 20	n.d.[c]
5	DIPEA (1.5)	CySH (0.2)	BPT (3)	DMF	22 : 55 : 5 : 18	37
6	DIPEA (1.5)	CySH (0.2)	BPT (3)	DMA	0 : 86 : 4 : 10	44
7	DIPEA (1.5)	CySH (0.2)	BPT (3)	DMSO	0 : 83 : 13 : 4	32
8	DIPEA (1.5)	CySH (0.2)	BPT (3)	THF	71 : 3 : 0 : 26	n.d.[c]
9	$Py{\cdot}BH_3$ (1.2)	–	BPT (3)	MeCN	78 : 2 : 4 : 16	n.d.[c]
10	AscH[d]/NEt_3 (1.5)	CySH (0.2)	BPT (3)	DMSO	0 : 75 : 0 : 25	14
11	γ-terpinene (1.5)	–	BPT (3)	DMA	0 : 90 : 0 : 10	72
12	**γ-terpinene (1.5)**	**CsF (1.0)**	**BPT (3)**	**DMA**	**0 : 98 : 0 : 2**	**80**
13	γ-terpinene (1.5)	CsF (1.0)	–	DMA	55 : 0 : 45 : 0	23
14[e]	γ-terpinene (1.5)	CsF (1.0)	BPT (3)	DMA	100 : 0 : 0 : 0	–[f]

[a] Determined by GC-MS analysis. [b] Determined by ^{19}F NMR with $PhCF_3$ as an internal standard. [c] Not determined. [d] AscH is ascorbic acid. [e] No light. [f] No reaction.

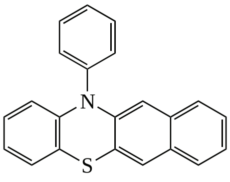
with full conversion (Table 1, entry 1). However, the competitive transformation of **2a** to difluoroalkene **4** and hydrodefluorination of the pyridine ring to form product **5** were observed (GC-MS analysis). The reaction in the presence of other photocatalysts such as 3DPA2FBN, $[Ir(dtbbpy)(ppy)_2]PF_6$ or $Ir(ppy)_3$ were notably less efficient (entries 2–4). The screening of solvents showed that *N*,*N*-dimethylacetamide (DMA) was the best medium (entries 5–8). The reaction with pyridine–borane complex instead of DIPEA proceeded slowly with predominant formation of product **5** (entry 9), while the use of ascorbic acid/triethylamine led to the target product **3a** in low yield (entry 10). Finally, the best results were obtained with γ-terpinene, a readily available terpene, which is expected to behave as efficient hydrogen atom source[36–39] (entries 11, 12). The formation of by-product **5** was mostly suppressed by addition of an equivalent amount of cesium fluoride, which, probably, inhibited dissociation of the corresponding radical anion to fluoride anion and an aryl radical. The reaction with γ-terpinene proceeded even in the absence of photocatalyst, though the outcome of this process was rather poor (entry 13). In a control experiment, no reaction was observed in the absence of light (entry 14).



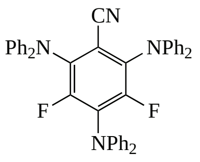
a R = $Ph(CH_2)_2$, $R_f = CF_3$
b R = $4\text{-}MeOC_6H_4(CH_2)_2$, $R_f = CF_3$
c R = $4\text{-}MeOC_6H_4(CH_2)_2$, $R_f = C_2F_5$
d R = $3,4,5\text{-}(MeO)_3C_6H_2(CH_2)_2$, $R_f = CF_3$
e R = $3,4,5\text{-}(MeO)_3C_6H_2(CH_2)_2$, $R_f = C_2F_5$
f R = $3\text{-}MeO_2C\text{-}4\text{-}MeOC_6H_3(CH_2)_2$, $R_f = CF_3$
g R = $3\text{-}MeO_2C\text{-}4\text{-}MeOC_6H_3(CH_2)_2$, $R_f = C_2F_5$

Scheme 3 *Reagents and conditions*: i, NaH (1.5 equiv.), C_5F_5N (1.2 equiv.), THF, 0 °C, 2 h; ii, γ-terpinene (1.5 equiv.), CsF (1.0 equiv.), BPT (3 mol%), $MeC(O)NMe_2$, 400 nm (80 W), 2 h.

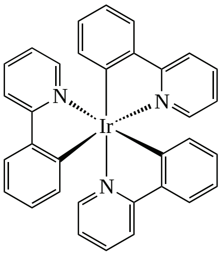
A series of compounds **2a–g** was prepared from the corresponding fluorinated alcohols **1a–g** by treatment with sodium hydride and pentafluoropyridine, and without purification they were subjected to the deoxygenation conditions (Scheme 3). Products **3a–g** were isolated mostly in moderate to good yields. In cases of C_2F_5-substituted compounds, the formation of significant amounts (*ca.* 10–15%) of alkene by-products of type **4** was detected by GC-MS analysis. The reaction of α-CF_3-substituted 4-benzyloxybenzylic alcohol led mostly to the products of the corresponding benzyl radical dimerization, and the reaction of a tertiary alcohol derived from acetophenone and $TMSCF_3$ gave complex mixture. In a reaction of *O*-tetrafluoropyridine ether derived from menthol, a non-fluorinated secondary alcohol, the starting substrate remained unconsumed under standard photocatalytic conditions.



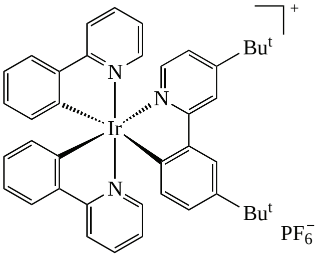
BPT



3DPA2FBN



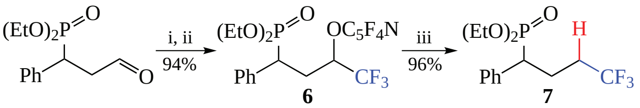
$Ir(ppy)_3$



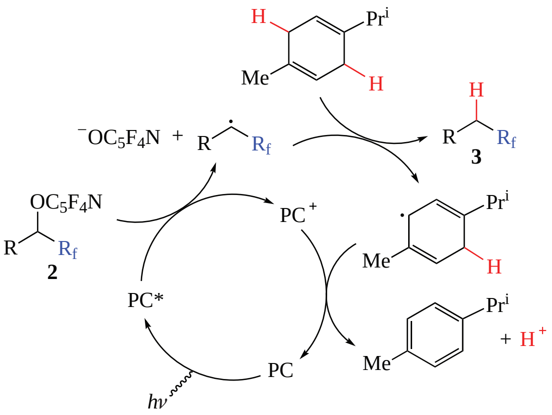
$[Ir(dtbbpy)(ppy)_2]PF_6$

As it was shown in our previous work,[34] compounds of type **2** may be generated from the corresponding aldehydes by a procedure of consecutive trifluoromethylation/fluoride-mediated nucleophilic substitution with pentafluoropyridine. We applied this protocol for the synthesis of phosphonate **6**, which was then deoxygenated with an overall yield of 90% based on the initial aldehyde (Scheme 4). This whole process may be carried out without isolation of **6** with 70% overall yield of **7**.

Based on the literature data and our previous studies, we propose the following mechanism (Scheme 5). Substrate **2** is reduced by excited photocatalyst (PC), and the resulting radical



Scheme 4 *Reagents and conditions*: i, Me_3SiCF_3 (1.2 equiv.), CsF (5 mol%), THF, –20 → 20 °C, 2 h; ii, C_5F_5N (1.5 equiv.), NEt_3 (20 mol%), room temperature, ~18 h; iii, γ-terpinene (1.5 equiv.), CsF (1.0 equiv.), BPT (3 mol%), $MeC(O)NMe_2$, 400 nm (80 W), 2 h.



Scheme 5

anion dissociates into a stable aryloxide anion and an alkyl radical. The radical is quenched by γ-terpinene giving product **3** and the corresponding dienyl radical. The latter quickly undergoes aromatization by oxidation with the photocatalyst.

In summary, a method of photocatalytic deoxygenation of α-fluoroalkyl-substituted alcohols using a readily available reducing agent is described. The intermediate tetrafluoropyridine ethers are prepared from the fluorinated alcohols and may be used without purification, or can be synthesized from the corresponding aldehydes in one step.

This work was supported by the Russian Science Foundation (grant no. 20-13-00112).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.04.028.

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Received: 7th December 2022; Com. 22/7065