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Single electron transfer approaches to the practical synthesis of aromatic and heterocyclic-CF_2H derivatives

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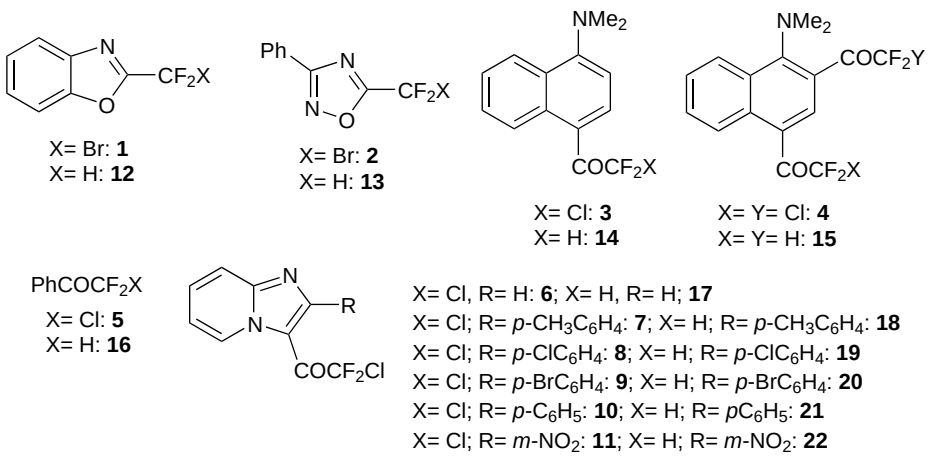
Abstract—Single electron transfer (SET) approaches with organic reductants such as sodium hydroxymethanesulfinate (Rongalite®), sodium dithionite (regarded as precursors of sulfoxylate radical anion) and tetrakis(dimethylamino)ethylene (TDAE) were employed for the reductive dehalogenation of a series of halogeno-difluoromethylated aromatics and heterocycles, and for the practical synthesis of the corresponding difluoromethylated derivatives. © 2001 Elsevier Science Ltd. All rights reserved.

There continues to be an interest in the synthesis of new fluorinated aromatics, heterocycles as well as fluorinated ketones because of their potential and biological properties.[1] The α,α-difluoroketones are of special interest as they have the capability to form hydrates and hemiketals.[1] It is believed that this property allows some fluorinated ketones to mimic the transition states involved in the hydrolytic action of many enzymes.[1] Fluorinated-substituted aromatics and heterocycles have found broad applications such as in agrochemicals, anticancer and antiviral agents.[2]

As part of our ongoing efforts in the search of new methodologies for the synthesis of fluorinated compounds with potential biological and synthetic applications,[3] we wish to report a mild and practical synthesis of aromatic and heterocyclic difluoromethylated derivatives **12**–**22** using halodifluoromethylated compounds **1**–**11**, as valuable starting materials (Scheme 1).[4] As it was anticipated that the carbon–halogen bond should be quite reactive in single electron transfer (SET) reactions both chemically and electrochemically, three different systems were employed and compared: sodium



Scheme 1.

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hydroxymethanesulfinate (Rongalite®), sodium dithionite, (regarded as precursors of sulfoxylate radical anion) and tetrakis(dimethylamino)ethylene (TDAE). Sodium hydroxymethanesulfinate (Rongalite®) as well as sodium dithionite ($Na_2S_2O_4$) are cheap and readily available materials. Reductive dechlorination reactions with Rongalite®[5a] and $Na_2S_2O_4$[5b] of various α-halogenated ketones have been previously reported but surprisingly only one example of their application to the synthesis of R-CF_2H derivatives is known.[6] Most frequently these reagents have been successfully used in free-radical addition and cyclization reactions with perfluoroalkyl halides as starting materials.[7] Tetrakis(dimethylamino)ethylene is also readily available and we have found that this organic reductant was useful for the in-situ generation of difluoromethyl and α,α-difluoroacetyl anions which participated in reactions of considerable synthetic utility.[8]

Among the different approaches tested, Rongalite® was found to be the best system in terms of yields and experimental procedure. Indeed with this reducing agent, solvent such as ethanol (reflux for 2–5 h as monitored by TLC) could be used with only 1.5 equiv. of the sulfoxylate radical anion precursor (3 equiv. were used to yield **15**); purification of the products was simple as only evaporation of the solvent and filtration through a short pad of silica gel was needed.[9] With sodium dithionite (1.2 equiv.), DMF/H_2O (4/1, v/v) was used as solvent at 65°C for 2 h. $NaHCO_3$ (1.2 equiv.) was also necessary to keep the reaction mixture slightly basic and to prevent decomposition of $Na_2S_2O_4$. Under these conditions, and with the chlorodifluoromethylated ketones as substrates, fluorine NMR of the crude product revealed formation of $RCHOHCF_2H$, as by-products, in 5–10% yields characterized by an ABXX′ system.[10] The TDAE approach (–20°C for 1 h and then room temperature for 2 h) also gives good yields of desired products after silica-gel chromatography; among the different solvents tested (acetonitrile, THF, toluene) DMF was the solvent of choice to get the higher yields.[11] For the sulfoxylate radical anion precursors, it is believed that an electron transfer between the starting material R-CF_2X and $SO_2^{\bullet-}$ (or HSO_2^-) occurs generating a difluoromethyl radical that is further reduced and protonated to give the final product (Scheme 2).

Dehalogenation reactions with TDAE involves the formation, at low temperature, of a deep-red charge transfer complex that dissociates readily after a stepwise electron transfer to the corresponding difluoromethyl anion with the formation of the insoluble $TDAE^{2+}$, $2X^-$ salt demonstrating that TDAE has been clearly oxidized (Scheme 3).

None of the yields have been optimized (Table 1) and room for improvement certainly exists. In addition the simplicity of the experimental procedures including purification of the products, cheapness and readily availability of the reagents makes these approaches quite attractive for organic chemists. Obviously other systems would have possibly worked for the dehalogenation reactions presented here:

- Zn/HOAc: acetic acid is used as solvent, and therefore, acid-catalyzed hydrolysis of the benzoxazole and oxadiazole rings (compounds **1**, **2, 12** and **13**) into the corresponding amides may have occurred.
- SmI_2/THF/HMPA: the cost of SmI_2 and the use of HMPA (toxic) as a co-solvent limits its practical use in industry.
- *n*-Bu_3SnH/AIBN: this system only works with the bromodifluoromethylated heterocycles **1** and **2** (not with the $RCOCF_2Cl$ substrates **3**–**11**) but trouble in removing tin impurities is a major drawback.

Therefore, our approaches are, in our mind, safer and more practical for the chemical industry and pharmaceutical companies, interesting in developing new strategies to the synthesis of fluorinated compounds. Work is under progress to use these derivatives in synthetic reactions.

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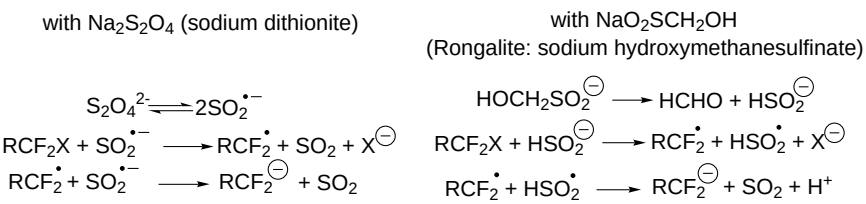
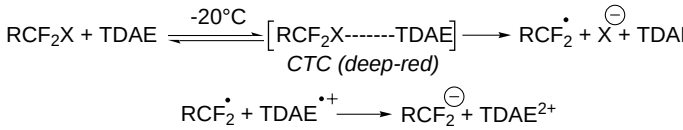


Scheme 2.



Scheme 3.

Table 1. Reductive dehalogenation syntheses of the R-CF_2H derivatives[a]

Substrates	System	Products (%)[b]	Spectral data[g]
1	$Na_2S_2O_4$[c]	**12**, 62	See Ref. 10
	Rongalite[d]	**12**, 68	
	TDAE[e]	**12**, 71	
2	$Na_2S_2O_4$[c]	**13**, 72	$\delta_F = -121.2$ (2F, d, $J = 57.4$ Hz); GC/MS: $M^+ = 196$, $M^+ - CF_2H = 145$
	Rongalite[d]	**13**, 65	
	TDAE[e]	**13**, 75	
3	$Na_2S_2O_4$[c]	**14**, 72	See Ref. 9
	Rongalite[d]	**14**, 68	
	TDAE[e]	**14**, 71	
4	$Na_2S_2O_4$[c,f]	**15**, 72	$\delta_F = -119.3$ (2F, d, $J = 57$ Hz), -123.2 (2F, d, $J = 52$ Hz); GC/MS: $M^+ = 327$, $M^+ - CF_2H = 276$
	Rongalite[d,f]	**15**, 68	
	TDAE[e,f]	**15**, 71	
5	$Na_2S_2O_4$[c]	**16**, 71	$\delta_F = -119.2$ (2F, d, $J = 57.2$ Hz); GC/MS: $M^+ = 156$, $M^+ - CF_2H = 105$
	Rongalite[d]	**16**, 63	
	TDAE[e]	**16**, 51	
6	$Na_2S_2O_4$[c]	**17**, 68	δ_F -126.3 (2F, d, $^2J_{F\text{-}H} = 55$ Hz). GC/MS: $M^+ = 196$, $M^+ - CF_2H = 145$.
	Rongalite[d]	**17**, 65	
	TDAE[e]	**17**, 71	
7	$Na_2S_2O_4$[c]	**18**, 72	See Ref. 11
	Rongalite[d]	**18**, 71	
	TDAE[e]	**18**, 66	
8	$Na_2S_2O_4$[c]	**19**, 65	δ_F -124.6 (2F, d, $^2J_{F\text{-}H} = 52.7$ Hz). GC/MS: $M^+ = 306$, $M^+ - CF_2H = 255$.
	Rongalite[d]	**19**, 62	
	TDAE[e]	**19**, 58	
9	$Na_2S_2O_4$[c]	**20**, 71	δ_F -124.5 (2F, d, $^2J_{F\text{-}H} = 52.7$ Hz). GC/MS: $M^+ = 350$, $M^+ - CF_2H = 299$.
	Rongalite[d]	**20**, 68	
	TDAE[e]	**20**, 70	
10	$Na_2S_2O_4$[c]	**21**, 65	δ_F -124.7 (2F, d, $^2J_{F\text{-}H} = 52.7$ Hz). GC/MS: $M^+ = 348$, $M^+ - CF_2H = 297$.
	Rongalite[d]	**21**, 62	
	TDAE[e]	**21**, 71	
11	$Na_2S_2O_4$[c]	**22**, 68	δ_F -124.0 (2F, d, $^2J_{F\text{-}H} = 52.7$ Hz). GC/MS: $M^+ = 317$, $M^+ - CF_2H = 266$.
	Rongalite[d]	**22**, 72	
	TDAE[e]	**22**, 62	

[a] All reactions were run under nitrogen with 1.76 mmol of starting material and 2.12 mmol of reductant.
[b] Isolated yields.
[c] DMF/H_2O (20 ml, 4/1 by volume) was used as solvent at 65°C for 2 h.
[d] Absolute EtOH (25 ml) was used as solvent under reflux (2 h for substrates **1**–**5** and 5 h for substrates **6**–**11**).
[e] Anhydrous DMF (5 ml) was used as solvent; –20°C for 1 h and room temperature for 2 h.
[f] 5.28 mmol of reductant was used.
[g] Fluorine NMR was taken in $CDCl_3$ (CCl_3F as internal reference).

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9. A typical procedure for the reaction between **3** and Rongalite® is as follows: Into a three-necked flask equipped with a reflux condenser (with a silica-gel drying tube) and a nitrogen inlet, were added under nitrogen, 25 ml of absolute EtOH followed by **3** (0.50 g, 1.76 mmol). The solution was stirred until complete dissolution and then Rongalite® (0.32 g, 2.12 mmol) was added. The whole mixture was then heated at reflux until complete consumption of starting material (2 h, TLC). The solution was filtered, and evaporated to dryness. The crude product was filtered through a short pad of silica-gel eluting with hexane/EtOAc (70:30) and recrystallized from hexane to give 0.31 g (1.19 mmol, 68%) of **14**. **4-Dimethylamino-naphthalen-1-yl-1-difluoroacetyl**: Mp = 70–72°C (yellow needles). ^{1}H NMR ($CDCl_3$): δ_H 3.07 (6H, s, -NMe_2), 6.44 (1H, t, -CF_2H, $^2J_{H-F}=57$ Hz), 6.92 (1H, d, H-2, $J=8.36$ Hz), 7.50–7.68 (2H, m, H-6 and H-7), 8.13–8.20 (2H, m, H-3 and H-8), 9.2 (1H, d, H-5, $J=8.38$ Hz). ^{19}F NMR ($CDCl_3$/$CFCl_3$): δ_F −119.31 (2F, d, $^2J_{F-H}=54$ Hz). GC/MS: $M^+=249$, $M^+-CF_2H=198$. Anal. calcd for $C_{14}H_{13}F_2NO$: C, 67.46; H, 5.22; N, 5.62. Found C, 67.68; H, 5.43; N, 5.87.
10. A typical procedure for the reaction between **1** and $Na_2S_2O_4$ is as follows: Into a three-necked flask equipped with a reflux condenser (with a silica-gel drying tube) and a nitrogen inlet, were added under nitrogen, 20 ml of DMF/H_2O (4/1, v/v) followed by **1** (0.44 g, 1.76 mmol). The solution was stirred until complete dissolution and then $Na_2S_2O_4$ (0.37 g, 2.12 mmol) followed by $NaHCO_3$ (0.18 g, 2.12 mmol) were added. The whole mixture was then heated at 65°C until complete consumption of starting material (2 h, TLC). The solution was hydrolyzed with H_2O (25 ml) and extracted with EtOAc (3×25 ml), the combined organic extracts washed with brine (3×25 ml) and dried over $MgSO_4$. Evaporation of the solvent left a yellowish viscous oil as crude product which was filtered through a short pad of silica gel eluting with hexane/EtOAc (80:20) to give 0.18 g (1.09 mmol, 62%) of **12** as a pale yellowish viscous liquid. **2-(Difluoromethyl)benzoxazole**: ^{1}H NMR (DMSO-d_6): δ_H 7.22–7.64 (1H, t, $^2J_{H-F}=52$ Hz, -CF_2H), 7.43–7.86 (4H, m, H-arom). ^{19}F NMR (DMSO-d_6/$CFCl_3$): δ_F −119.8 (2F, d, $^2J_{F-H}=52.1$ Hz). GC/MS: $M^+=169$, $M^+-CF_2H=118$. Anal. calcd for $C_8H_5F_2NO$: C, 56.81; H, 2.98; N, 8.28. Found C, 56.74; H, 3.03; N, 8.15.
11. A typical procedure for the reaction between **7** and TDAE is as follows: Into a two-necked flask equipped with a silica-gel drying tube and a nitrogen inlet was added, under nitrogen at −20°C, 5 ml of anhydrous DMF and then **7** (0.56 g, 1.76 mmol). The solution was stirred and maintained at this temperature for 30 min and then was added dropwise (via a syringe) the TDAE (0.42 g, 2.12 mmol). A red color immediately developed with the formation of a white fine precipitate. The solution was vigorously stirred at −20°C for 1 h and then warmed up to room temperature for 2 h. After this time TLC analysis (EtOAc–hexane, 90–10) clearly showed that **7** was totally consumed. The orange–red turbid solution was filtered (to remove the octamethyloxamidinium dichloride) and hydrolyzed with 30 ml of H_2O. The aqueous solution was extracted with $CHCl_3$ (3×30 ml), the combined organic solutions washed with brine (3×30 ml), H_2O (3×30 ml) and dried over $MgSO_4$. Evaporation of the solvent left a yellowish viscous liquid as crude product. Purification by silica-gel chromatography (EtOAc–hexane, 90–10 as eluent) gave 0.33 g (1.16 mmol, 66%) of **18** as pale–yellowish crystals: **2,2-Difluoro-1-(2-*p*-tolyl-imidazo[1,2-*a*]pyridin-3-yl)-ethanone**. ^{1}H NMR ($CDCl_3$): δ_H 2.45 (3H, s, CH_3), 5.80–6.07 (1H, t, $^2J_{H-F}=52.7$ Hz, -CF_2H), 7.21–7.23 (1H, m, H-6), 7.33–7.35 (2H, AA′BB′, H-arom), 7.49–7.51 (2H, AA′BB′, H-arom), 7.65–7.67 (1H, m, H-7), 7.81–7.83 (1H, d, $J=8.85$ Hz, H-8), 9.75–9.76 (1H, d, $J=6.94$ Hz, H-5). ^{19}F NMR ($CDCl_3$/$CFCl_3$): δ_F −124.8 (2F, d, $^2J_{F-H}=52.7$ Hz). GC/MS: $M^+=286$, $M^+-CF_2H=235$. Anal. calcd for $C_{16}H_{12}F_2N_2O$: C, 67.13; H, 4.23; N, 9.79. Found C, 67.34; H, 4.03; N, 9.83.