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Tetrakis(dimethylamino)ethylene (TDAE) mediated addition of difluoromethyl anions to heteroaryl thiocyanates. A new simple access to heteroaryl–SCF_2R derivatives

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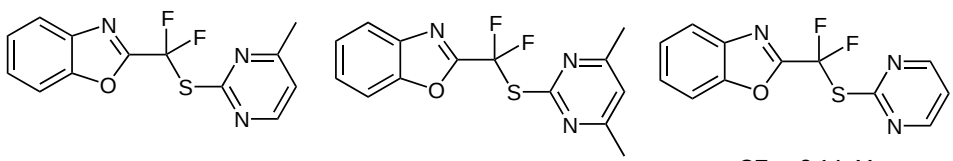
Abstract—New heteroaryl–SCF_2R derivatives **8–13** are easily obtained in one-pot from the tetrakis(dimethylamino)ethylene (TDAE) mediated reduction of halogenodifluoromethyl substrates RCF_2X **1–4** in the presence of heteroaryl–thiocyanates **5–7**.

There continues to be an interest in the synthesis of new *gem*-difluorinated compounds because of the potential biological properties of such molecules.[1] Fluorinated-substituted aromatics and heterocycles, may find broad applications as 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 recently synthesized a series of R-CF_2SAr derivatives, via the $S_{RN}1$ methodology, with bromodifluoromethylated heterocycles[4] and chlorodifluoromethylated ketones[5] and commercially available aromatic and heterocyclic sulfur nucleophiles. Some of the derivatives were found to be active against the HIV-1 virus (Scheme 1).[4]

Despite the fact that the $S_{RN}1$ methodology was efficient for the synthesis of a series of -CF_2S- derivatives, the reaction was limited to commercially available heteroaryl–sulfur nucleophiles.

Previous studies from our group[6a,b] have shown that CF_3S derivatives could be prepared from the corresponding thiocyanate precursors on treatment with the Ruppert's reagent (CF_3TMS) in the presence of catalytical amount of tetra-*n*-butylammonium fluoride; on the other hand, we have presented an efficient access to heteroaryl–difluoromethylated compounds, via the tetrakis(dimethylamino)ethylene (TDAE) mediated reduction of the corresponding halogenodifluoromethylated substrates in the presence of electrophiles.[7] These recent studies, including the earlier work of Wakselman et al.[6c,d] (for the addition of perfluoroalkyl carbanions to thiocyanates and isocyanates) prompted us to use the TDAE methodology to prepare new heteroaryl–SCF_2R derivatives that could complement our recent $S_{RN}1$ reactions. In such a way, a new series of $ArSCF_2R$ derivatives **8–13** were obtained in moderate to good



Scheme 1.

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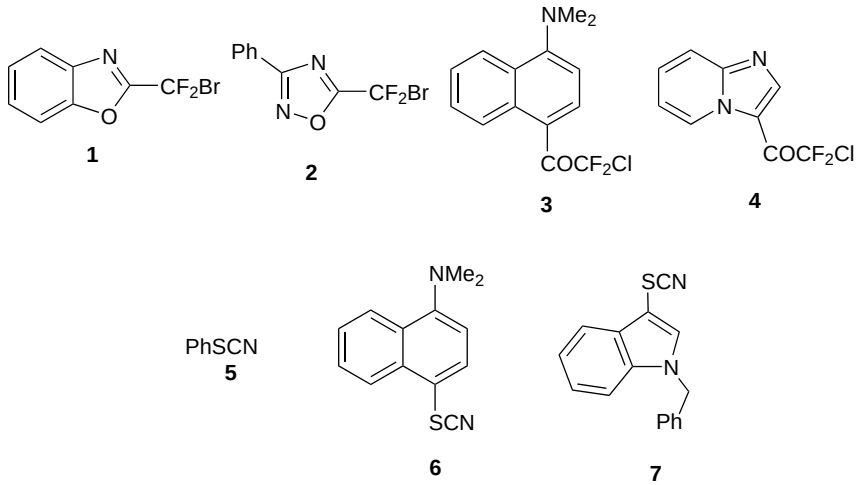
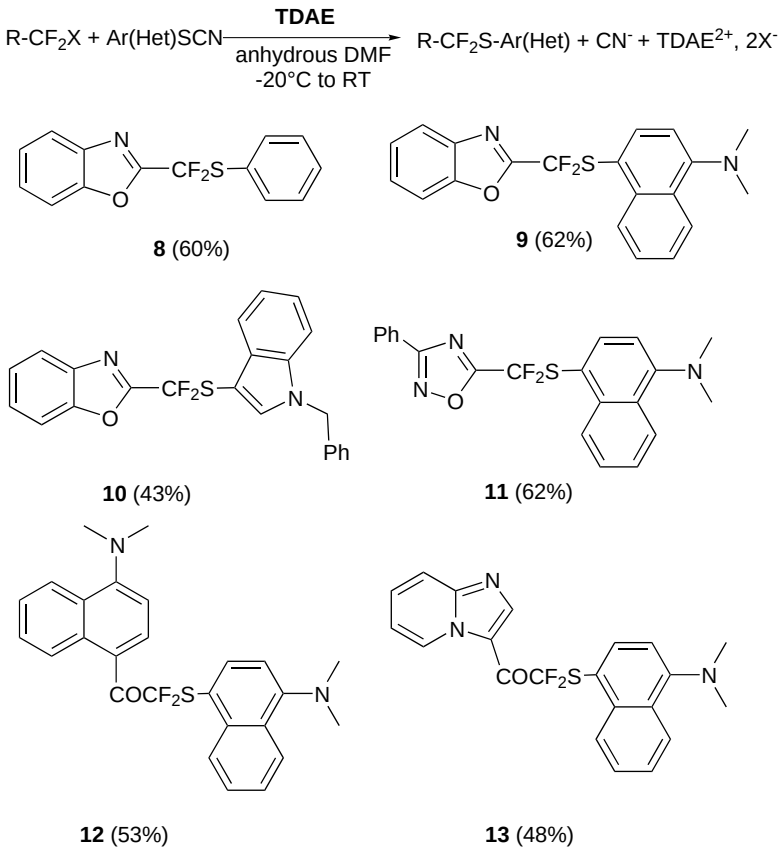
yields from the corresponding bromodifluoromethylated heterocycles **1** and **2**,[8] chlorodifluoromethyalted ketones **3** and **4**[9] and subsequent trapping with heteroaryl thiocyanate precursors **5**–**7** (Scheme 2).[10]

An equimolar amount of TDAE was necessary for complete reduction of the starting RCF_2X, with the reaction being almost complete after 2 hours (TLC monitoring). With the RCF_2Br substrates, an equimolar amount of thiocyanates, and for the $RCOCF_2Cl$ a slight excess (1.2 equiv.), was necessary for a complete conversion. At the end of the reaction, the corresponding insoluble $TDAE^{2+}$, $2X^-$ salt is recovered, demonstrating that the TDAE has been clearly oxidized. The ArSCN derivatives were not reduced by the TDAE (to yield the corresponding thiolates which could induce a $S_{RN}1$ reaction), since their reduction potentials were found to be relatively high (for example PhSCN is reduced in DMF/0.1 M NBu_4PF_6 at a potential close to −2.1 V versus SCE). All the products were obtained as solid (**8**) or viscous oils (**9**–**13**) after purification by silica gel chromatography (Scheme 3).[11] None of the



Scheme 2.



Scheme 3.

yields have been optimized and room for improvement certainly exists. The only side-products which represent the remaining balance material were the hydrogenolysis compounds RCF_2H resulting from protonation of the difluoromethyl anions. In some cases, small amount of fluorinated impurities were observed by fluorine NMR of the crude products (these polar compounds not yet identified, were easily removed during the column chromatography purification).

In conclusion, to the best of our knowledge, this is the first report of the electron transfer substitution reactions of heteroaryl thiocyanate derivatives with halogenodifluoromethylated compounds, and the application to the facile synthesis of a series of CF_2S derivatives. The products are of special interest as potential HIV-1 inhibitors[4] and, from the recent literature,[12] these derivatives could also find some application as agrochemicals. Work is under progress to extend this methodology to other halogenodifluoromethylated compounds including new aromatics and heterocycles. Further chemical elaboration with these derivatives will be done in a due course.

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11. A typical procedure for the reaction between **1**, **6** and TDAE is as follows: Into a three-necked flask equipped with a calcium chloride drying tube, and a nitrogen inlet was added, under nitrogen, 5 ml of anhydrous DMF and then **1** (0.50 g, 2.0 mmol) followed by **6** (0.45 g, 2 mmol). The solution was cooled down to −20°C, stirred and maintained at this temperature for 30 min and then the TDAE (0.40 g, 2.0 mmol) was added dropwise (via a syringe). 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 (brown–red color). After this time TLC analysis (EtOAc–petroleum ether, 85:15) clearly showed that **1** was totally consumed. The brown turbid solution was filtered (to remove the octamethyloxamidinium dibromide) and hydrolyzed with 30 ml of an aqueous NaCl solution. The aqueous solution was extracted with CH_2Cl_2 (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 brown–red viscous liquid as crude product. Fluorine NMR shown that the desired -CF_2S substituted product was obtained (a singlet at −75.8 ppm/$CFCl_3$) with some reduction product (a doublet at −120 ppm/$CFCl_3$) in a ratio 6.5/0.6. Other minor fluorinated impurities were observed around −110 to −120 ppm/$CFCl_3$. Purification by silica gel chromatography (EtOAc–petroleum ether, 90:10 as eluent) gave 0.46 g (1.24 mmol, 62%) of **9** as an orange viscous liquid (solidifies in the freezer): **[4-(Benzooxazol-2-yl - difluoro - methanesulfinyl) - naphthalen - 1 - yl] - dimethylamine**. ^{1}H NMR ($CDCl_3$): δ_H 2.86 (3H, s,CH_3), 6.93 (1H, d, H-2, J = 8.42 Hz), 7.26–32 (4H, H-arom of benzoxazole), 7.52–7.66 (2H, m, H-6 and H-7), 8.16–8.28 (2H, m, H-3 and H-8), 9.01 (1H, dd, H-5, J = 7.69, 0.65 Hz). ^{19}F NMR ($CDCl_3$/$CFCl_3$): δ_F −75.6 (2F, s). GC/MS: M^+ = 370, M^+–$SC_{10}H_6NMe_2$ = 169. HRMS calcd for $C_{20}H_{16}F_2N_2OS$: 370.0951; found: 370.0965.
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