Polyfluoroalkylation of pyrrole with 1,2-dibromotetrafluoroethane activated by sulfur dioxide

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A possibility of the homogeneous catalytic fluoroalkylation of pyrrole with Freon $BrCF_2CF_2Br$ using a nitrous base—sulfur dioxide system was shown. The influence of pK_a of bases on the occurrence of these processes was studied. The ion-radical mechanism of the processes was substantiated.

Key words: Freons, fluoroalkylation, pyrrole, sulfur dioxide.

Search for new methods for the introduction of per- and polyfluoroalkyl groups into heterocyclic compounds attracts considerable interest of many researchers, since these products can be used as biologically active compounds.[1—5] One of the promising sources of polyfluoroalkyl groups can be Freons containing along with fluorine atoms several atoms of other halogens, which substantially extends their synthetic potentialities.[6—10] However, as known, Freons possess very low reactivity and are inert toward many organic substrates, which requires the search for and the use of various methods of activation of the organic substrate—Freon interaction by increasing the reactivity of either the molecule that must be fluoroalkylated, or Freon (the latter is usually carried out by the generation of highly reactive free fluoroalkyl radicals from Freon).

In the case of azoles, the introduction of perfluoroalkyl groups is carried out mainly involving perfluoroalkyl radicals, which are generated from perfluoroalkyl halides photochemically,[3,11] electrochemically,[12,13] and by the chemical interaction of Freons with derivatives of tetravalent sulfur.[2,14—18] As a rule, perfluoroalkyl iodides with much higher reactivity than Freons were used as fluoroalkylating agents, and azole salts with alkaline metals were fluoroalkylated instead of azoles themselves.[6,7,19]

The purpose of the present work is to reveal a possibility of the fluoroalkylation of pyrrole (instead of its salts) with Freon $BrCF_2CF_2Br$ by the introduction of the $—CF_2CF_2Br$ group under mild conditions. These objects of the study were chosen, because pyrrole and its derivatives find wide use in synthetic practice and the synthesis of its derivatives containing the $—CF_2CF_2Br$ group can provide routes for further modification involving the bromine atom.

We have earlier shown[16,17,19] that the fluoroalkylation with Freons of such organic substrates as thiophenols or phenols (ArXH, X = S, O) can successfully be activated using simultaneously organic bases and electron transfer mediators from the substrate to Freon with the generation from the latter of highly reactive fluoroalkyl radicals. Substituted pyridines were used as organic bases, because they are capable of hydrogen bonding with the SH and OH groups and, hence, enhancing the electron-donor ability of ArXH due to the equilibrium shift

$$ArXH \rightleftharpoons [ArX^- + H^+]$$

toward thiophenolate and phenolate anions (in the composition of the ionic complex) with a lower oxidation potential. However, only this effect was insufficient for the process to occur, and mediators (SO_2, I_2, *etc.*) were introduced to provide electron transfer.[17—19]

An analogous approach has well recommended itself and makes it possible to efficiently and rather selectively perform fluoroalkylation processes with high yields of target products. We used this approach to study a possibility of pyrrole fluoroalkylation under mild conditions taking into account that pyrrole, as phenols and thiophenols, can form hydrogen bonds with bases, although the latter are weaker.[20]

It was found that under usual conditions pyrrole in DMSO does not react with Freon $BrCF_2CF_2Br$, because pyrrole cannot reduce Freon or detach from it the positivated bromine atom. The introduction of various pyridines into the solution enhances the electron-donor ability of pyrrole. However, this ability is still insufficient for the spontaneous electron transfer from pyrrole to Freon and its activation to occur. A different pattern is observed when sulfur dioxide, *viz.*, an electron transfer mediator, is added to the system considered. In this case, pyrrole fluoroalkylation with the formation of 2-(2-bromotetrafluoroethyl)pyrrole can be performed rather efficiently (Scheme 1, Table 1).[21]

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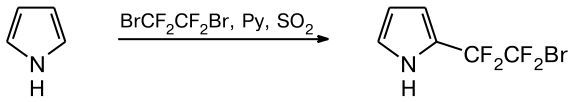
Scheme 1



Since sulfur dioxide plays the key role in the fluoroalkylation of pyrrole with Freon $BrCF_2CF_2Br$, we studied the dependence of the yield of 2-(2-bromotetrafluoroethyl)pyrrole on the SO_2 concentration. It was found that with an increase in the SO_2 concentration the yield of the fluoroalkylation products increases (see Table 1) and reaches 85% in experiments with twofold SO_2 excess over the amount of pyrrole taken in the reaction. The yield of the target fluoroalkylation product decreases with the further addition of SO_2, which can be due to a decrease in the basicity of the medium with high SO_2 concentration.

To reveal the route of the predominant fluoroalkylation of pyrrole with 1,2-dibromotetrafluoroethane (*via* the radical or ionic (halophilic)[6,7,19] mechanism), we studied the influence of traps of free radicals on the yield of fluoroalkylation products. It was established that the addition of a radical trap, in particular, *p*-dinitrobenzene, results in the complete inhibition of the process, and no products of pyrrole polyfluoroalkylation are observed (see Table 1), which indicates the radical route of their formation.

As mentioned above and as follows from the data in Table 1, the absence of nitrous bases in the solution does not allow one to obtain target products, which indicates a significance of the basicity of the medium for the successful occurrence of pyrrole fluoroalkylation with $BrCF_2CF_2Br$. Therefore, we studied in more detail the influence of bases, *viz.*, pyridine with various pK_a (the pK_a values concern the conjugated acids of the pyridines studied), on the yields of polyfluoroalkylated pyrroles (Table 2).

We failed to carry out the fluoroalkylation of pyrrole with Freon $BrCF_2CF_2Br$ in the presence of weak bases (2-chloropyridine and 2-acetylpyridine), whereas in the presence of β-picoline (pK_a = 5.97) and 2,5-lutidine (pK_a = 6.25) the process occurs very efficiently, and the yield of 2-(2-bromotetrafluoroethyl)pyrrole becomes almost quantitative (see Table 2). The results obtained indicate that pyridine with rather high pK_a values (5.23 and higher) should be used for the fluoroalkylation to occur, and the optimum yields are observed at pK_a close to 6. It should be mentioned that the yield of the target fluoroalkylation product decreases and small amounts (8%) of olefin $F_2C{=}CF_2$ are formed upon the reaction of pyrrole with Freon in the presence of γ-collidine (see Table 2). This can be associated with the deactivation of the electron transfer mediator (SO_2) due to precipitation in the presence of γ-collidine as a result of the interaction of sulfur dioxide with collidine. One of the reasons for the formation of tetrafluoroethylene along with the target fluoroalkylation product can be the debromination of Freon $BrCF_2CF_2Br$ due to its two-electron reduction in the pyrrole—γ-collidine—sulfur dioxide system.

As mentioned above, the fluoroalkylation of pyrrole with Freon $BrCF_2CF_2Br$ was predetermined by the fact that the use of a nitrous base—sulfur dioxide system allows one to activate Freon by the electron transfer from pyrrole to SO_2 and then to Freon to form active radicals $^{\cdot}CF_2CF_2Br$ capable of fluoroalkylating pyrrole. To elucidate whether the above presented fluoroalkylation process can proceed *via* this route and whether sulfur dioxide can accept an electron from pyrrole and to transfer it to Freon, we carried out spectrophotometric and electrochemical studies of particular steps of the process.

The electronic absorption spectra of the electrochemically generated $SO_2^{-\cdot}$ radical anion and the products of its "dimerization" with the initial SO_2 have been studied earlier.[22] It was shown that the absorption band with a maximum at 485 nm corresponds to the $SO_2^{-\cdot}$ radical anion, and the $S_2O_4^{-\cdot}$ radical anion (λ_{max} = 580 nm) formed by the $SO_2^{-\cdot}$ radical anion and the starting sulfur dioxide is more stable. Taking into account these facts,

Table 1. Dependence of the yield of the product of pyrrole polyfluoroalkylation with Freon $BrCF_2CF_2Br$, 2-(2-bromotetrafluoroethyl)pyrrole, on the SO_2 concentration*

$[SO_2]$	[β-Picoline]	$[BrCF_2CF_2Br]$	Yield of product (%)
	10^{-3} mol		
—	10	4.0	—
0.5	10	4.0	18
1.0	10	4.0	51
2.0	10	4.0	85
4.0	10	4.0	55
2.0	10	4.0	—**
1.0	10	1.0	78
1.0	—	4.0	—

* [Pyrrole] = $1 \cdot 10^{-3}$ mol; 25 °C; DMSO.
** The radical trap (*p*-dinitrobenzene) was added.

Table 2. Dependence of the yield of the product 2-(2-bromotetrafluoroethyl)pyrrole on the nature of substituted pyridines*

Pyridine	pK_a	Yield of product (%)
2-Chloropyridine	0.72	—
2-Acetylpyridine	3.18	—
Pyridine	5.23	78
β-Picoline	5.97	89
2,5-Lutidine	6.25	95
γ-Collidine	7.60	62**

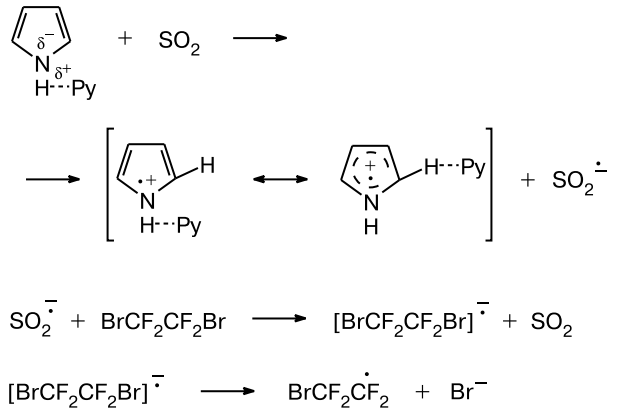
* [Pyrrole] = $0.5 \cdot 10^{-3}$ mol; $[SO_2] = 0.44 \cdot 10^{-3}$ mol; $[BrCF_2CF_2Br] = 0.8 \cdot 10^{-3}$ mol; [Substituted pyridine] = $= 1.0 \cdot 10^{-2}$ mol.
** In this case, $F_2C{=}CF_2$ (8%) is also found in the products.

we studied the electronic absorption spectra of sulfur dioxide in DMSO under the following conditions: (1) with the addition of pyrrole, (2) with the addition of β-picoline in the absence of pyrrole, and (3) in the presence of pyrrole and β-picoline. It was found that neither pyrrole, nor β-picoline can reduce SO_2 to form the $SO_2^{-\cdot}$ radical anion or its dimeric form $S_2O_4^{-\cdot}$. A different situation was observed when two components (pyrrole and β-picoline) were simultaneously added to a solution of SO_2. In this case, the solution (in the absence of Freon) turned blue, and an absorption band with a maximum at 580 nm appeared in the electronic spectrum, indicating the formation of the $S_2O_4^{-\cdot}$ radical anion under these conditions. Thus, as follows from the results of out spectrophotometric studies, sulfur dioxide can withdraw electrons from pyrrole in the presence of β-picoline. At the same time, the addition of Freon $BrCF_2CF_2Br$ to the reaction mixture results in an almost instant disappearance of the blue color of the solution, which can be due to the interaction of the $S_2O_4^{-\cdot}$ radical anion with Freon. The electronic absorption spectra of the pyrrole—β-picoline—sulfur dioxide—Freon system exhibit no $SO_2^{-\cdot}$ radical anion or its adduct with SO_2—$S_2O_4^{-\cdot}$.

The ability of the $SO_2^{-\cdot}$ radical anion that formed (or its adduct $S_2O_4^{-\cdot}$) to transfer an electron to Freon with the regeneration of the starting SO_2 and to act thus as an electron transfer mediator from pyrrole to Freon in the fluoroalkylation process considered is confirmed by the results of our voltammetric studies. It was shown[16,17] that considerable catalytic currents caused by the electron transfer by sulfur dioxide from the cathode to Freon appear during the electrochemical reduction of SO_2 in polar aprotic organic solvents, including DMSO, in the presence of Freon $BrCF_2CF_2Br$.

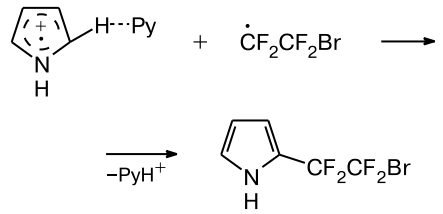
Based on the performed complex of spectrophotometric and electrochemical studies, the initiation of pyrrole fluoroalkylation with Freon $BrCF_2CF_2Br$ can be presented by Scheme 2, where Py is pyridine and its derivatives.

Scheme 2



The further development of the process is not evident. Thus generated bromotetrafluoroethyl radical can further react with the pyrrole radical cation (its complex with substituted pyridines), and the subsequent proton elimination affords 2-(2-bromotetrafluoroethyl)pyrrole (Scheme 3).

Scheme 3



In this process, either the bromide ion, or pyridine can act as a proton acceptor. It cannot be excluded that the fluoroalkylation process can proceed *via* the radical nucleophilic mechanism of the $S_{RN}1$ type,[12,23—25] which can result in the *C*-fluoroalkylation of nitrogen-containing heterocycles.[12,26]

Experimental

Dimethylformamide was distilled and stored above sieves A4. Pyrrole was distilled prior to use. ^1H and ^{19}F NMR spectra were recorded on a Bruker-CXP-90 spectrometer (relative to Me_4Si and CCl_3F, respectively). Electronic spectra were measured on a Specord M-10 spectrometer.

A. **Reaction of $BrCF_2CF_2Br$ with pyrrole in the presence of sulfur dioxide and β-picoline.** A solution of sulfur dioxide in DMF ($SO_2 = 5 \cdot 10^{-4}$—$4 \cdot 10^{-3}$ mol) was added to freshly distilled pyrrole (0.067 g, $1 \cdot 10^{-3}$ mol) in DMF or DMSO (0.5 mL) with β-picoline (0.4 mL, $1 \cdot 10^{-2}$ mol) purged with argon. After addition of Freon $BrCF_2CF_2Br$ (0.48 mL, $4 \cdot 10^{-3}$ mol) the total volume of the reaction mixture was brought to 2 mL by DMF. The mixture was stored in a sealed ampule for 4—6 h at 35 °C, and then the contents of the ampule was poured into an aqueous solution of hydrochloric acid (17%), which was extracted with hexane or chloroform 4—5 times. The organic layer was washed with water and dried over K_2CO_3, and the solvent was distilled off. The residue was distilled *in vacuo*. 2-(2-Bromotetrafluoroethyl)pyrrole with b.p. 66—68 °C (15 Torr) was obtained. ^1H NMR ($CDCl_3$), δ: 6.2 (1 H, H(4)); 6.5 (1 H, H(3)); 7.0 (1 H, H(5)); 11.9 (1 H, NH). ^{19}F NMR (DMSO-d_6), δ: 65.7 (t, 2 F, CF_2, J = 5.6 Hz); 102.8 (t, 2 F, CF_2, J = 5.6 Hz). Found (%): C, 29.5; H, 1.7; N, 5.8. $C_6H_4BrF_4N$. Calculated (%): C, 29.3; H, 1.6; N, 5.7.

B. **The reaction of $BrCF_2CF_2Br$ with pyrrole in the presence of sulfur dioxide and *p*-dinitrobenzene** was carried out according to a procedure similar to procedure *A* with the addition of *p*-dinitrobenzene (0.040 g, $0.3 \cdot 10^{-3}$ mol) to the solution.

C. **The reaction of $BrCF_2CF_2Br$ with pyrrole in the presence of sulfur dioxide and various substituted pyridines** was carried out *via* a procedure similar to procedure *A* but with the addition of the corresponding substituted pyridine instead of β-picoline to the solution.

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