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Pyridine•BrF_3, the Missing Link for Clean Fluorinations of Aromatic Derivatives

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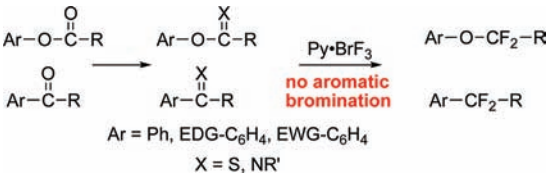
ABSTRACT



This work demonstrates the unique features of the never used before Py•BrF_3 complex in the field of aromatic organic fluorinations. The main disadvantage of the noncomplexed BrF_3 is the fact that usually, in addition to the desired fluorination, a parallel electrophilic aromatic bromination takes place as well. Use of the Py•BrF_3 complex reduces this electrophilic bromination, which is observed with most reagents based on fluorine and bromine [BrF].

Bromine trifluoride could be used as a powerful brominating agent of aromatic rings including very deactivated ones.[1] However, when it comes to fluorinating processes of precursors containing aromatic rings this becomes a major drawback since the parallel electrophilic aromatic bromination considerably reduces the effectiveness of the reagent. Such a process may also occur with 70% HF/py and 1,3-dibromo-5,5-dimethylhydantoin (DBH) serving as a source for a [BrF] reagent.[2] In order to reduce the electrophilicity of the bromine it has to be coordinatively bonded to a molecule which on one hand will offer basic electrons to this soft acidic halogen and on the other will not destroy the molecule as is the case with water, THF, and other compounds containing a basic oxygen atom. It occurred to us that there is a good chance that a complex with pyridine will deliver satisfactory results since the electrophilic power of the bromine should be quite reduced while the pyridine resistance to electrophilic attacks will keep it from destroying the bromine trifluoride itself. Only once, about 40 years ago, the complex, Py•BrF_3, has been briefly mentioned without ever finding any synthetic use.[3] It is readily prepared by mixing molar equivalent amounts of BrF_3 and pyridine in $CHCl_3$ or $CFCl_3$ resulting in a white precipitate. No isolation or further purification is required for use in the synthetic methods described below.

Our hope was that while the pyridine in Py•BrF_3 will considerably reduce the electrophilicity of the bromine, the electronic cloud of an aromatic ring would be potent enough to bring and hold the reagent in its vicinity forcing it to react with soft bases such as sulfur or nitrogen attached to it (Scheme 1). Such a combination should ensure an ionic character of a reaction, placing the nucleophilic fluorides (which are now even more potent than in BrF_3 itself) near the electrophilic carbon center and readily fluorinate it.

Thus when we reacted Py•BrF_3 with 4-chlorophenyl chlorothioformate (**1**) the desired 1-chlorodifluoromethoxy-4-chlorobenzene (**2**)[4] was obtained in 80% yield without forming any bromo-aromatic byproduct. It should be noted that the same reaction, performed under the same conditions, with BrF_3 gave **2** in only 40% yield accompanied by quite a few brominated products (Table 1).[4] Furthermore, when Py•BrF_3 was brought in contact with 4-propylphenyl chlorothioformate (**3**),[5] the 1-chlorodifluoromethoxy-4-propylbenzene (**4**) was formed in 80% yield without any damage to the aromatic nucleus or to the aliphatic chain. This reinforces the notion that during

(1) Rozen, S.; Lerman, O. *J. Org. Chem.* **1993**, *58*, 239.
(2) Matthews, D. P.; Whitten, J. P.; McCarthy, J. R. *Tetrahedron Lett.* **1986**, *27*, 4861.
(3) Naumann, D.; Lehmann, E. *J. Fluorine Chem.* **1975**, *5*, 307.
(4) Hagooly, Y.; Sasson, R.; Welch, M. J.; Rozen, S. *Eur. J. Org. Chem.* **2008**, 2875.
(5) McKay, A. F.; Garmaise, D. L.; Paris, G. Y.; Gelblum, S.; Ranz, R. J. *Can. J. Chem.* **1960**, *38*, 2042.

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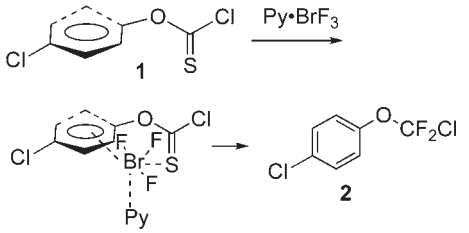
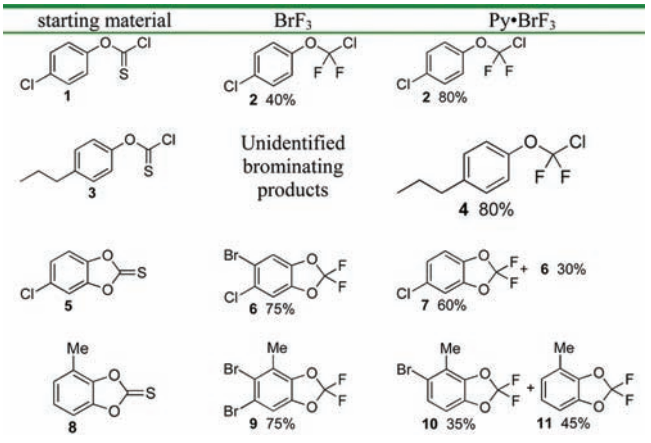
the reaction, Py•BrF_3 is loosely attached to the aromatic ring since, as we will see below, with purely aliphatic substrates no clean reaction takes place. It should be noted that compound **4** is somewhat hydrolytically sensitive, slowly turning in the open air to the respective chloroformate derivative $PrC_6H_4OC(O)Cl$.[6]

Scheme 1



Other types of aromatic substrates also emphasize the advantage of the Py•BrF_3 complex. 5-Chlorobenzo-1,3-dioxole-2-thione (**5**) is more activated toward electrophilic attack than **1**, but still its reaction with suspension of the solid complex of Py•BrF_3 resulted in the desirable 5-chloro-2,2-difluorobenzo-1,3-dioxole (**7**) in 60% yield. For comparison, only the monobromo product **6** was formed when BrF_3 alone was used.[7] A similar trend was observed in the case of the highly activated 4-methylbenzo-1,3-dioxole-2-thione (**8**). With bromine trifluoride, only 5,6-dibromo-2,2-difluoro-4-methylbenzo-1,3-dioxole (**9**)[7] was isolated in 75% yield. With the Py•BrF_3 complex, two products were obtained. The first was the desirable nonbrominated 2,2-difluoro-4-methylbenzo-1,3-dioxole (**11**) in 45% yield accompanied by the monobrominated product 5-bromo-2,2-difluoro-4-methylbenzo-1,3-dioxole (**10**) in 35% yield showing that Py•BrF_3 has lower bromination potential, although it is not completely void when highly activated aromatic rings are present (Table 1).

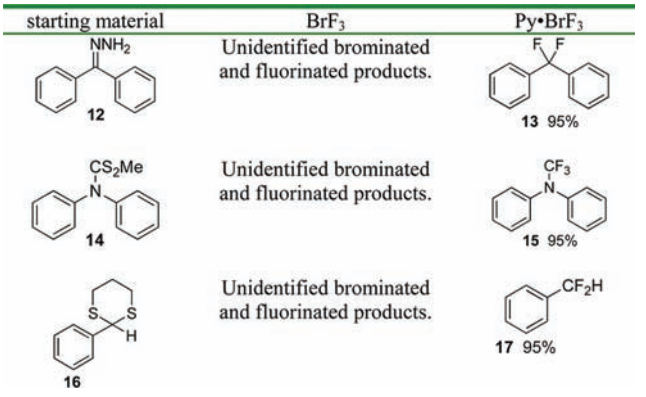
Table 1. Replacing Aromatic C=S Moiety with the CF_2 Group



(6) Buehlmayer, P.; Breitenstein, W.; Furet, P.; Pirard, B.; Von M. A.; Zoller, T. PCT Int. Appl. 2008, 87 pp. CAN 148:426904.

Reactions of aliphatic hydrazones,[8] *N*-xanthates,[9] or 2-alkyl-1,3-dithianes[10] with BrF_3 gave satisfactory results, but parallel reactions with aromatic substrates such as **12**, **14**, and **16** further expose the differences between the BrF_3 and the Py•BrF_3 complex. When each of these compounds was reacted with BrF_3, no selective fluorination reactions were observed and unidentified mixtures of products containing bromine and fluorine were obtained. With the Py•BrF_3 complex, however, the desired difluorodiphenylmethane (**13**), *N*-phenyl-*N*-(trifluoromethyl)aniline (**15**), and (difluoromethyl)benzene (**17**) were formed as single products in excellent yields (Table 2).

Table 2. Replacing Aromatic C=N and C—S Moieties with the CF_2 Group



In the aliphatic series the situation was reversed and the advantage of the noncomplexed BrF_3 was quite clear. The strong electrophilic bromine in the BrF_3 enables a better complexation of the reagent with the sulfur−carbon center as in the tris(methylthio) derivative **18** followed by selective fluorination, to produce the 7-chloro-1,1-difluoroheptane (**19**) in 70% yield.[11] When the Py•BrF_3 complex was reacted with the same compound, only a mixture of unidentified fluorinated products was obtained. Similar results were observed with the dithiane aliphatic derivative **20**, which reacted selectively with BrF_3 to produce 2-(3,3-difluoropropyl)bicyclo[2.2.1]heptane (**21**)[10] in 65% yields but gave an unidentified mixture when the Py•BrF_3 complex was used (Table 3). Such behavior is the result of the decreased electrophilicity of Py•BrF_3 responsible for its inability to efficiently complex itself around the sulfur−carbon center, resulting in random radical fluorination and bromination reactions in a similar way as BrF_3 does with regular paraffins. This, however, does not have to happen with all aliphatic moieties. When an aliphatic chain was attached to an aromatic ring, which may serve as an additional anchor, the chain was not affected, and as

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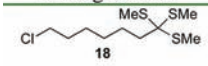
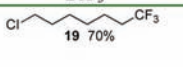
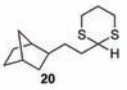
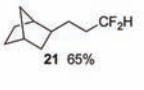
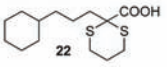
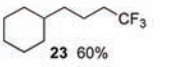
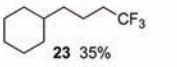
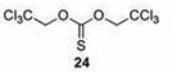
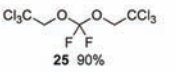
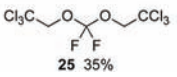
(8) Rozen, S.; Mishani, E.; Bar-Haim, A. *J. Org. Chem.* **1994**, *59*, 2918.
(9) Hagooly, Y.; Gatenyo, J.; Hagooly, A.; Rozen, S. *J. Org. Chem.* **2009**, *74*, 8578.
(10) Sasson, R.; Hagooly, A.; Rozen, S. *Org. Lett.* **2003**, *5*, 769.
(11) Hagooly, A.; Rozen, S. *J. Fluorine Chem.* **2005**, *126*, 1239.

mentioned above, compound **3** was transformed to **4** with Py•BrF_3 in very good yield.

The trend of radical pathways governing pure aliphatic derivatives when using Py•BrF_3 could be further demonstrated by comparison with other reactions of BrF_3 utilizing such routes. When reacting BrF_3 with 1,3-dithiane-2-carboxylic acids such as **22**, a two-step mechanism governs the reaction, with one step being of a radical nature and responsible for the formation of **23** in 60% yield.[12] It is reasonable to assume that this is the reason for retaining some of the selectivity when **22** was reacted with the Py•BrF_3 complex forming **23** although this time in 35% yield only. Similarly, when the halogenated backbone of **24**, which partially prevents radical side reactions, was reacted with Py•BrF_3, **25**[13] was formed in 35% yield. This is lower than the yield obtained with BrF_3 alone (Table 3), meaning that while radical reactions were kept low, they nevertheless exist with Py•BrF_3 especially when it lacks good anchors.

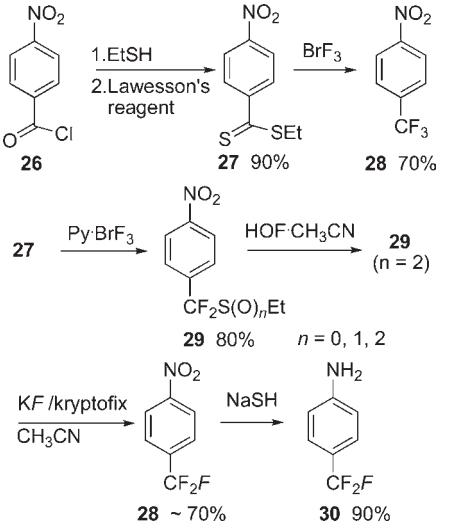
Table 3. Comparing Aliphatic Reactions with BrF_3 and Py•BrF_3

starting material	BrF_3	Py•BrF_3
 **18**	 **19** 70%	Unidentified fluorinated products
 **20**	 **21** 65%	Unidentified fluorinated products
 **22**	 **23** 60%	 **23** 35%
 **24**	 **25** 90%	 **25** 35%

An interesting benefit of the reactions with the Py•BrF_3 complex emerged when considering the field of Positron Emission Tomography (PET). This is a noninvasive technique using isotopes such as ^{18}F for the diagnostic of cancer, myocardial problems, brain diseases, and much more.[14] This powerful tool has spread rapidly, and today, almost every major hospital has PET facilities, for either pure medicinal or research uses, or both. The best mimic for the naturally found hydrogens is the ^{18}F radionuclide making it very popular in this field.

The importance of the CF_3 group in medicinal chemistry is well-known, and quite a few important drugs contain this group. However, very few examples in the literature describe a CF_3 group labeled with ^{18}F, and all of those suffer from very low chemical and especially radiochemical yields. We used the less reactive Py•BrF_3 complex to create $ArCF_2SR$ (or $ArOCF_2SR$) intermediates, which after the oxidation of the sulfur atom may serve as a precursor for various $ArCF_3$ compounds.[15] Indeed, the HOF•CH_3CN complex[16] turns the above sulfides into a good leaving sulfone group in a fast and usually quantitative reaction (Scheme 2).[17] This can be demonstrated by using 4-nitrobenzoyl chloride (**26**) which, with Lawesson's reagent, produced the dithioester **27**.[18] When this intermediate was reacted with BrF_3 it resulted in 1-nitro-4-(trifluoromethyl)benzene (**28**) which is a dead end as far as a labeling process with regards to ^{18}F is concerned. When, however, **27** was reacted with the more tamed Py•BrF_3 complex, a mixture of the corresponding sulfide, sulfoxide, and traces of sulfone **29** was formed. This mixture was treated with HOF•CH_3CN, rapidly transferring all sulfur-containing compounds to the sulfone **29** (n = 2), which contains the desired leaving sulfonyl group. This compound was subjected to KF and kryptofix, conditions that mimic the ^{18}F labeling, and the desirable 1-nitro-4-(trifluoromethyl)benzene (**28**) was obtained in 70% yield. The reduction of the nitro to the amine group proceeded quickly, and **30**, which could be made now with ^{18}F, was formed in good yield and may be tagged to a variety of biological active compounds (Scheme 2).

Scheme 2



In conclusion, this work demonstrates the unique features of the Py•BrF_3 complex especially in the field of aromatic fluorinations. Its main advantage is reducing the parallel electrophilic bromination process, which frequently accompanies reactions with reagents based on fluorine and bromine. It also opens new possibilities for

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(15) Rozen, S.; Mishani, E. *J. Chem. Soc., Chem. Commun.* **1994**, 2081.
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(18) (a) Yousif, N. M.; Pedersen, U.; Yde, B.; Lawesson, S. O. *Tetrahedron* **1984**, *40*, 2663. (b) Rozen, S.; Mishani, E. *J. Chem. Soc., Chem. Commun.* **1993**, 1761.

constructing the CF_3 group that contains the important ^{18}F isotope for use in PET.

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Supporting Information Available. Complete experimental section including ^{1}H, ^{13}C, ^{19}F NMR and data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.