Synthesis of difluoroaryldioxoles using BrF_3

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A novel synthesis of different aromatic and heteroaromatic difluorodioxole derivatives has been developed. The starting materials were catechols, which, after treatment with thiophosgene, formed at 0 °C the respective thiodioxoles. The latter were reacted for a short time with commercially available bromine trifluoride, producing potentially biologically important difluoroaryldioxoles in moderate to high yields.

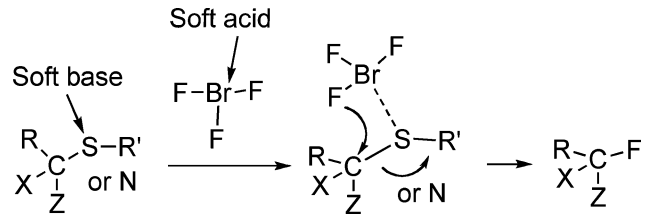
Introduction

Difluoroaryldioxoles are rapidly emerging as materials possessing remarkable biological properties.[1] In the medical field, many members of this group are considered potential chemotherapeutic agents,[2] while in agriculture, it has been found that the properties which make some compounds good fungicides, insecticides and herbicides are considerably enhanced by the difluoromethylenedioxy moiety.[3]

The most widely used synthetic method for preparing diflurobenzodioxoles is the fluorine–chlorine exchange reaction using various forms of hydrogen fluoride.[4] A very few diflurobenzodioxoles have also been prepared by oxidative desulfurization–fluorination using n-$Bu_4NH_2F_3$.[5] Recently, we prepared a series of aliphatic difluoromethylene diethers, which were too easily hydrolyzed.[6] We describe here a synthetic method for the preparation of the far more stable aromatic difluoromethylene dioxides from readily available catechols using bromine trifluoride (BrF_3).

Although commercial, BrF_3 is not a common reagent in organic laboratories, and many do not feel at ease using it because of its high reactivity. However, under the right conditions, it can be used as an efficient fluorinating agent for various heteroatoms,[7] as well as an important tool for producing modern anaesthetics,[8] transforming carbonyls to the CF_2 group[9] and converting alkyl halides into the CHF_2 moiety.[10] It has also been used for the synthesis of hexafluorocyclopentadiene,[11] for the preparation of the rare OCF_2Cl[12] and OCF_2H[13] moieties, for achieving difficult to obtain aromatic brominations[14] and for quite a few other transformations.[15]

The major reason for the high reactivity of BrF_3 is its weak Br–F bonds, which can encourage indiscriminate radical reactions.[16] In order to avoid such pathways, a soft base (usually involving a sulfur or nitrogen atom) has to be present in the target molecule in order to form a complex with the softly acidic bromine atom[17] and thus place its fluorides near the site where the substitution is planned (Scheme 1). It should be emphasized that this proximity, and the fact that the fluorides are non-solvated, is responsible for very fast substitution reactions (usually less than a minute) that are quite uncharacteristic for reactions involving nucleophilic fluorination. The short reaction times point toward the potential these reactions have for labelling compounds with the appropriate radiochemical nuclides, [18]F and [76]Br, for positron emitting tomography (PET) research and diagnostics.



Scheme 1 General mechanism for specific reactions of BrF_3 with compounds possessing soft base elements.

Results and discussion

In order to provide the necessary anchor for BrF_3, we treated catechols with thiophosgene, resulting in the corresponding aromatic thiocarbonates. Thus, for example, a suspension of 850 mg (6.3 mmol) of 5-cyanocatechol (**1**) was treated with 1.7 g of Na_2CO_3 in 15 mL of water, followed by the dropwise addition of 0.6 mL (7.8 mmol) of thiophosgene. The reaction mixture was then stirred at room temperature for 2 h, resulting in 2-thioxobenzo-1,3-dioxole-5-carbonitrile (**2**) in a nearly quantitative yield. Thiocarbonate **2** was then reacted with one mole equivalent of BrF_3 dissolved in 10 mL of cold (0 °C) $CFCl_3$. A practically instantaneous reaction took place, forming 2,2-difluorobenzo-1,3-dioxole-5-carbonitrile (**3**)[18] in 90% yield (Scheme 2).

Similarly, 5-carboethoxycatechol (**4**) was converted to 2-thioxobenzo-1,3-dioxole-5-carboethoxylate (**5**)[5] in excellent yield. The reaction of **5** with BrF_3 resulted in 2,2-difluorobenzo-1,3-dioxole-5-ethyl carboxylate (**6**),[18] again in excellent yield.

BrF_3 is a strong oxidizer and it can, for example, oxidize alcohols to acyl fluorides.[19] It was of interest to see how an aldehyde function behaved under the present conditions. We started with 3,4-dihydroxybenzaldehyde (**7**) and converted it, as in the above cases, to 2-thioxobenzo-1,3-dioxole-5-carbaldehyde (**8**) in a practically quantitative yield. The sulfur atom of this thiocarbonate proved to be a very potent anchor for the soft bromine of the reagent leading, through a very fast reaction, to corresponding 2,2-difluoro-1,3-dioxole-5-carbaldehyde (**9**)[18] in excellent yield before the reagent had a chance to oxidize the aldehyde moiety.

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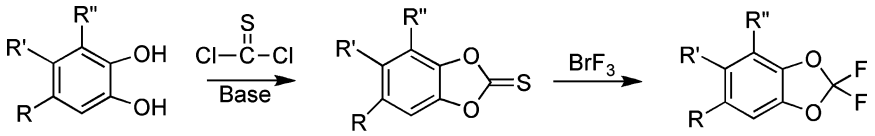


1 R = CN; R' = R'' = H **2** (95%) **3** R = CN; R' = R'' = H (90%)

4 R = COOEt; R' = R'' = H **5** (95%) **6** R = COOEt; R' = R'' = H (90%)

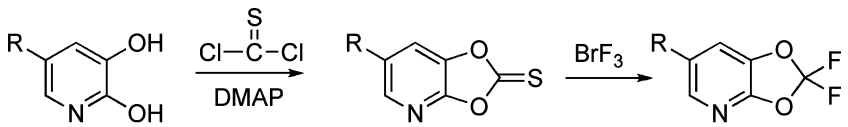
7 R = CHO; R' = R'' = H **8** (95%) **9** R = CHO; R' = R'' = H (95%)

10 R = Cl; R' = R'' = H **11** (95%) **12** R = Cl; R' = Br; R'' = H (90%)

13 R = R' = H; R'' = Me **14** (95%) **15** R = R' = Br; R'' = Me (75%)

16 R = $BocNHCH_2CH_2$; R' = R'' = H **17** (95%) **18** R = Br; R' = FCH_2; R'' = H (80%)

Scheme 2 Synthesis of difluorobenzodioxoles.



19 R = H **20** 90% **21** 95%

22 R = Cl **23** 95% **24** 95%

Scheme 3 Heteroaromatic difluorodioxoles.

While compounds possessing deactivated rings behaved as expected, those that were activated or mildly deactivated toward electrophilic attack were, in addition to creating the difluorodiether moiety, also ring brominated, since BrF_3 is a potent electrophilic brominating agent.[14] Thus, 3,4-dihydroxychlorobenzene (**10**) was converted to 5-chlorobenzo-1,3-dioxole-2-thione (**11**), and when reacted with BrF_3, 5-bromo-6-chloro-2,2-difluorobenzo-1,3-dioxole (**12**) was formed and isolated in good yield.[18] In order to bring this reaction to completion 2 mole equivalents of the reagent had to be employed, since less than this amount led to a mixture of **12** and starting thiocarbonate **11**. When starting with more activated aromatic rings, such as 4-methylcatechol (**13**), which was successfully transformed into 4-methylbenzo-1,3-dioxole-2-thione (**14**), the bromination process was more intensive and the only isolable compound proved to be 5,6-dibromo-2,2-difluoro-4-methylbenzo-1,3-dioxole (**15**) in 75% yield.

A somewhat puzzling reaction, for which we do not have a full explanation at present, was observed when we considered 4-(2-aminoethyl)benzene-1,2-diol (**16**) as a substrate. Since the NH_2 group has to be protected, we prepared the Boc derivative, **16**, which was successfully converted to respective thiocarbonate **17**. When **17** was reacted with BrF_3, the difluoromethylenedioxo moiety was indeed formed but the protecting group was also cleaved, along with a methylene unit, to produce novel 5-bromo-2,2-difluoro-6-(fluoromethyl)benzo-1,3-dioxole (**18**) in 80% yield. We suspect the involvement of a radical pathway, producing a stable benzyl radical, but have no direct proof for such a process at this time.

The reaction is also operable with heteroaromatics such as pyridine derivatives. 2,3-Dihydroxypyridine (**19**) was easily converted by thiophosgene to the unknown 1,3-dioxolo-4,5-pyridine-2-thione (**20**) in high yield. Applying BrF_3 led to the expected 2,2-difluoro-1,3-dioxolo-4,5-pyridine (**21**) in high yield. Compound **21**, however, is unstable under common conditions (open air and humidity) and we were able to identify it only by ^1H NMR, ^{19}F NMR and Amirav's supersonic GC-MS method, which is able to rapidly reveal the molecular parent ion where all other methods fail.[20] It should be mentioned that when Leroux converted the unsubstituted hydroxypyridine to the corresponding trifluoromethyl ether, it also proved to be unstable.[21] As a result, we turned our attention to substituted pyridines, which usually provide much more stable compounds. We reacted 5-chloro-2,3-dihydroxypyridine (**22**) with thiophosgene and obtained 6-chloro-1,3-dioxolo-4,5-pyridine-2-thione (**23**) in excellent yield. Despite the basic nitrogen, BrF_3 reacts first with the thione moiety, yielding 95% of stable 6-chloro-2,2-difluoro-1,3-dioxolo-4,5-pyridine (**24**) (Scheme 3).

Conclusion

BrF_3 offers a very efficient method for the preparation of aromatic difluorodioxoles, which are interesting and promising compounds in pharmacology today. As with elemental fluorine not many years ago, chemists may realize that, under the right conditions, BrF_3 can be a very useful reagent and should not be avoided at any cost, as is the situation in many laboratories at present.

Experimental section

^{1}H NMR spectra were recorded using either 200 or 400 MHz spectrometers with $CDCl_3$ as the solvent and Me_4Si as the internal standard. ^{19}F NMR spectra were measured at 188.1 MHz with $CFCl_3$ serving as the internal standard. Proton broadband decoupled ^{13}C NMR spectra were recorded at either 50.2 or 100.5 MHz. Here too, $CDCl_3$ served as the solvent and Me_4Si as the internal standard. MS samples were measured under CI conditions. In cases where this method could not detect the molecular ion, we successfully used Amirav's supersonic GC-MS technique. In these cases, we used isotope abundance analysis, which provided very satisfactory results, as shown for the specific compounds. This type of analysis confirmed the proposed elemental formulas as it ranked them in first place and hence as the best choice, with very good matching factors of better than 860 (out of 999).[20] Silica gel 60H (Merck) and petroleum ether/dichloromethane or ethyl acetate were used for flash chromatography.

Preparing and handling of BrF_3

Although commercially available, we prepared BrF_3 simply by passing 0.6 mol of commercial fluorine (*ca.* 95%) through 0.2 mol of bromine placed in a copper reactor and held at temperatures between 4–10 °C. Under these conditions, the higher oxidation state of bromine, BrF_5, does not form in any appreciable amount.[22] Since practically all the fluorine is consumed during the reaction, as was evident from the very small amount of F_2 found at the outlet of the reactor (determined by an iodometric method), it could be concluded that the reaction was complete. The reagent could be stored in Teflon® containers indefinitely. BrF_3 tends to react very exothermically with water and oxygenated organic solvents such as acetone or THF. Alkanes, like petroleum ether, cannot serve as a solvent either since they too react rapidly with BrF_3. Solvents such as $CHCl_3$, CH_2Cl_2, $CFCl_3$ or, if solubility is not an issue, any perfluoroalkane or perfluoroether may be used. Any use of BrF_3 should be conducted in a well-ventilated area, and caution and common sense should be exercised.

At this point we would like to clarify that when dealing with BrF_3, all the mole equivalent values stated in this work are approximate since the reagent usually contains some bromine. What is more, no matter what the solvent is, it will slowly react with the reagent, effectively reducing somewhat the amount of BrF_3 reaching the substrate.

Procedure for the preparation of aromatic thiocarbonate derivatives (2, 5, 8, 11, 14, 17, 20 and 23)

6.3 mmol of the corresponding catechol was dissolved in 15 mL of water and 1.7 g of sodium carbonate (Na_2CO_3). The suspension was cooled to 0 °C, 0.6 mL (7.8 mmol) of thiophosgene was added dropwise and then the mixture stirred for 2 h. The product was isolated by filtration and purified by flash chromatography. In the case of the pyridine derivatives (**20** and **23**) 12.6 mmol of 4-(dimethylamino)pyridine (DMAP) was used as the base and 40 mL dichloromethane as the solvent. The data given below is only for the non-commercial derivatives.

2-Thioxobenzo-1,3-dioxole-5-carbonitrile (2). Prepared starting with 3,4-dihydroxybenzonitrile (**1**) (850 mg), as described above, in 95% yield: 1.1 g, white crystals, m.p. = 105.4–105.9 °C; ^{1}H NMR 7.67 (1 H, dd, J_1 = 8 Hz, J_2 = 1.5 Hz), 7.63 (1 H, d, J = 1.5 Hz), 7.45 ppm (1 H, d, J = 8 Hz); ^{13}C NMR 182.3, 149.0, 146.2, 131.2, 117.4, 114.2, 111.6, 110.1 ppm. The usual MS methods failed to show any molecular peak, but Amirav's method revealed a strong molecular ion peak of m/z 177 $(M)^+$ with an isotope abundance analysis matching factor of 998 out of 999.

2-Thioxobenzo-1,3-dioxole-5-carbaldehyde (8). Prepared from 3,4-dihydroxybenzaldehyde (**7**) (870 mg), as described above, in 95% yield: 1.1 g, white crystals, m.p. = 105.7–106.1 °C; ^{1}H NMR 9.99 (1 H, s), 7.88 (1 H, dd, J_1 = 8 Hz, J_2 = 1.5 Hz), 7.81 (1 H, d, J = 1.5 Hz), 7.47 ppm (1 H, d, J = 8 Hz); ^{13}C NMR 189.7, 183.2, 150.1, 147.0, 134.7, 129.6, 110.9, 110.2 ppm. The usual MS methods failed to show any molecular peak. However, by using Amirav's method, we could see a strong molecular ion peak of m/z 180 $(M)^+$ with an isotope abundance analysis matching factor of 975 out of 999.

4-Methylbenzo-1,3-dioxole-2-thione (14). Prepared from 3-methylbenzene-1,2-diol (**13**) (780 mg), as described above, in 95% yield: 1 g, white crystals, m.p. = 107.8–108.6 °C; ^{1}H NMR 7.22 (1 H, t, J = 8 Hz), 7.13 (2 H, t, J = 8 Hz), 2.45 ppm (3 H, s); ^{13}C NMR 184.5, 145.8, 145.0, 127.4, 125.6, 121.7, 107.8, 14.8 ppm. HRMS (CI) m/z calc. for $C_8H_6O_2S$ 167.0167 $(MH)^+$, found 167.0176 $(MH)^+$.

***tert*-Butyl 2-(2-thioxobenzo-1,3-dioxol-5-yl)ethylcarbamate (17).** Prepared from *tert*-butyl 3,4-dihydroxyphenethylcarbamate (**16**)[23] (1.6 g), as described above, in 95% yield: 1.8 g, white crystals, m.p. = 142.7–143.1 °C; ^{1}H NMR 7.29 – 7.21 (3 H, m), 4.67 (1 H, s br), 3.42 (2 H, t, J = 7 Hz), 2.92 (2 H, t, J = 7 Hz), 1.47 ppm (9 H, s); ^{13}C NMR 184.9, 156.6, 146.7, 145.3, 138.5, 126.8, 111.3, 110.8, 80.3, 42.5, 36.9, 29.1 ppm. The usual MS methods failed to show any molecular peak. However, by using Amirav's method, a strong molecular ion peak of m/z 295 $(M)^+$ was revealed with an isotope abundance analysis matching factor of 999 out of 999.

1,3-Dioxolo-4,5-pyridine-2-thione (20). Prepared from pyridine-2,3-diol (**19**) (700 mg), as described above, in 90% yield: 865 mg, white crystals, m.p. = 82.3–83.8 °C; ^{1}H NMR 8.23 (1 H, dd, J_1 = 6 Hz, J_2 = 1.5 Hz), 7.63 (1 H, dd, J_1 = 8 Hz, J_2 = 1.5 Hz), 7.33 ppm (1 H, dd, J_1 = 8 Hz, J_2 = 6 Hz); ^{13}C NMR 181.2, 155.6, 144.4, 138.9, 122.1, 118.5 ppm. The usual MS methods failed to show any molecular peak, but Amirav's method revealed a strong molecular ion peak of m/z 153 $(M)^+$.

6-Chloro-1,3-dioxolo-4,5-pyridine-2-thione (23). Prepared from pyridine-2,3-diol (**22**) (916 mg), as described above, in 95% yield: 1.1 g, white crystals, m.p. = 98.5–99.0 °C; ^{1}H NMR 8.24 (1 H, d, J = 2.3 Hz), 7.72 ppm (1 H, d, J = 2.3 Hz); ^{13}C NMR 181.2, 154.5, 143.7, 139.4, 130.4, 119.3 ppm. The usual MS methods failed to show any molecular peak. With Amirav's method we detected a strong molecular ion peak of m/z 186.9 $(M)^+$ with an isotope abundance analysis matching factor of 999 out of 999.

General procedure for the preparation of difluoromethylenedioxo derivatives with BrF_3

The 1,3-dioxole-2-thione derivatives were dissolved in 20–25 mL of $CHCl_3$ in a glass flask and cooled to 0 °C. One mole equivalent

of BrF_3 was dissolved in 10 mL of $CFCl_3$, cooled to 0 °C and added dropwise (about 1 min) at the same temperature using a glass dropping funnel. The reaction mixture was then washed with aqueous Na_2SO_3 until colorless, the aqueous layer extracted three times with CH_2Cl_2 and the combined organic layers dried over $MgSO_4$. Evaporation of the solvent followed by flash chromatography yielded the desired fluorinated compounds.

5,6-Dibromo-2,2-difluoro-4-methylbenzo-1,3-dioxole (15). Prepared from 4-methylbenzo-1,3-dioxole-2-thione (**14**) (1 g), as described above, in 75% yield: 1.5 g, yellow crystals, m.p. = 52.9–53.7 °C; ^{1}H NMR 7.20 (1 H, s), 2.37 ppm (3 H, s); ^{13}C NMR 142.6, 131.8 (t, J = 254 Hz), 128.9, 123.2, 121.9, 118.8, 112.0, 17.3 ppm; ^{19}F NMR −50.1 ppm (2 F, s). The usual MS methods failed to show any molecular peak. Amirav's supersonic GC-MS revealed a strong molecular ion peak of m/z 328 $(M)^+$. It should be mentioned that along with **15**, some traces of mono- and tribrominated difluoromethylenedioxo derivatives were also observed and identified by their respective MS spectra.

5-Bromo-2,2-difluoro-6-(fluoromethyl)benzo-1,3-dioxole (18). Prepared from 4-methylbenzo-1,3-dioxole-2-thione (**17**) (1.8 g), as described above, in 80% yield: 1.3 g, colorless oil; ^{1}H NMR 7.36 (1 H, s), 7.29 (1 H, s), 5.50 ppm (2 H, d, J_{HF} = 47 Hz); ^{13}C NMR 144.7, 144.3, 132.6, 132.4 (t, J = 260 Hz), 114.9, 114.5, 110.1, 83.8 ppm (d, J = 172 Hz); ^{19}F NMR −48.3 (2 F, s), −214.3 ppm (1 F, t, J_{HF} = 47 Hz). The usual MS methods failed to show any molecular peak. Amirav's method revealed a strong molecular ion peak of m/z 267.9 $(M)^+$ with an isotope abundance analysis matching factor of 998 out of 999. Anal. calc. for $C_8H_4BrF_3O_2$: C, 35.72; H, 1.50; Br, 29.70; F, 21.19. Found: C, 35.54; H, 1.41; Br, 30.13; F, 21.31.

2,2-Difluoro-1,3-dioxolo-4,5-pyridine (21). Prepared from 1,3-dioxolo-4,5-pyridine-2-thione (**20**) (865 mg), as described above, in 95% yield: 856 mg, colorless oil; ^{1}H NMR 7.89 (1 H, dd, J_1 = 5 Hz, J_2 = 1.5 Hz), 7.33 (1 H, dd, J_1 = 8 Hz, J_2 = 1.5 Hz), 7.06 ppm (1 H, dd, J_1 = 8 Hz, J_2 = 5 Hz); ^{13}C NMR 153.1, 141.2, 136.7, 129.5 (t, J = 269 Hz), 119.7, 116.7 ppm; ^{19}F NMR −50.5 ppm (2 F, s). This compound is very volatile and unstable, meaning that the usual MS methods failed to show any molecular peak. The supersonic GC-MS method revealed a strong molecular ion peak of m/z 159 $(M)^+$.

6-Chloro-2,2-difluoro-1,3-dioxolo-4,5-pyridine (24). Prepared from 1,3-dioxolo-4,5-pyridine-2-thione (**23**) (1.1 g), as described above, in 95% yield: 1.1 g, colorless oil; ^{1}H NMR 7.96 (1 H, d, J = 2 Hz), 7.43 ppm (1 H, d, J = 2 Hz); ^{13}C NMR 152.3, 140.8, 137.7, 130.6 (t, J = 260 Hz), 128.1, 118.3 ppm; ^{19}F NMR −49.9 ppm (2 F, s). As with the previous cases, the usual MS methods fail to show any molecular peak. However, by using Amirav's method, we were able to detect a strong molecular ion peak of m/z 193 $(M)^+$ with an isotope abundance analysis matching factor of 995 out of 999. Anal. calc. for $C_6H_2ClF_2NO_2$: Cl, 18.32; F, 19.63; N, 7.24. Found: Cl, 18.33; F, 18.87; N, 6.86.

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