Bromination of Deactivated Aromatics Using BrF_3 without a Catalyst

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Brominated aromatic compounds are important in the pharmaceutical industry, as fire retardants, herbicides, biocides, and various intermediates in organic synthesis. Most aromatic bromination processes are carried out in the presence of various Lewis acids serving as catalysts. Their main disadvantage is the requirement for anhydrous conditions and especially for the large amount of catalyst needed, which often results in substantial amounts of effluents discharged, raising serious disposal problems. Furthermore, bromination of aromatic compounds, in particular nonactivated ones, is a time-consuming process with relatively low yields. The other well-known route consists of the diazotation of the corresponding anilines, followed by thermal decomposition in the presence of bromide ion. This usually requires relatively long reaction times and a suitable aniline derivative which is not always easily available.

Not long ago we suggested a different route for such brominations, based on BrF made in situ directly from the corresponding elements.[1] Although this method resulted in excellent yields, its disadvantages for a large-scale synthesis were the low temperatures ranging between −45 and −78 °C and the considerable quantities of solvents. What is more, a setup for working with fluorine had to be physically attached to the bromination process since the BrF could not be stored and had to be constantly generated. As a result, relatively small batches of aromatic compounds were brominated by this method.

Bromine trifluoride is a commercial compound very easily made just by passing slightly more than 3 equiv of fluorine over bromine at 0 °C. Still, like elemental fluorine up to 15 years ago, organic chemists have shied away from its use. Fewer than 10 papers dealing with its synthetic potential in organic chemistry have appeared out of some 200 works with BrF_3 found in the whole chemical literature. These papers concentrate on fluorinations, some nucleophilic[2] and some electrophilic, mainly on tertiary C–H bonds,[3] but never relate to purposes such as aromatic bromination. Such reactions require, of course, a strong electrophilic bromine species, while BrF_3 has electrophilic fluorines.

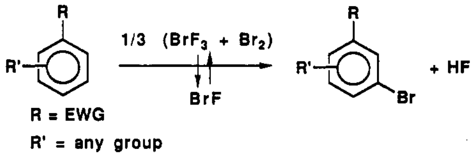
In order to suppress the electrophilicity of the fluorine we added a slight excess of bromine since the easy to achieve equilibrium[4] of $BrF_3 + Br_2 = 3BrF$ should be beneficial to the brominating process by creating a strong positively polarized bromine. The question was then which electron donor, the added bromine molecule or the π electrons of an aromatic compound, would react faster with BrF_3. For activated derivatives such as toluene, anisol, or acetanilide the answer was clearly in favor of the ring. Such compounds reacted immediately, giving a complex mixture of fully and partially fluorinated compounds each in a few percent yield. Much milder activated rings, such as chlorobenzene, were better substrates favoring electrophilic bromination but still with yields no higher than 25% (see Table I).

Table I

starting material	product	yield (%)
$C_6H_5NO_2$	*m*-$BrC_6H_4NO_2$	80
C_6H_5CN	*m*-BrC_6H_4CN[a]	45
$C_6H_5CF_3$	*m*-$BrC_6H_4CF_3$	65
C_6H_5COOMe	*m*-BrC_6H_4COOMe	65
C_6H_5Cl	*p*-BrC_6H_4Cl[b]	25
1,3-$(COOEt)_2C_6H_4$	3,5-$(COOEt)_2C_6H_3Br$	55
1,2-$(COOEt)_2C_6H_4$	2,3-$(COOEt)_2C_6H_3Br$ +	35
	3,4-$(COOEt)_2C_6H_3Br$	35
3-$NO_2C_6H_4COCH_3$	3-Br-5-$NO_2C_6H_4COCH_3$[c]	85[d]
4-$NO_2C_6H_4COCH_3$	2-Br-4-$NO_2C_6H_4COCH_3$[c]	90
4-$NO_2C_6H_4CH_3$	2-Br-4-$NO_2C_6H_4CH_3$[c]	40
1,4-$(COOMe)_2C_6H_4$	2,5-$(COOMe)_2C_6H_3Br$[c]	55
1,3-$(NO_2)_2C_6H_4$	3,5-$(NO_2)_2C_6H_3Br$[c]	65

[a] An additional 12% of the *o*-bromo derivative was also identified. [b] An additional 5% of the *m*-bromo derivative was also identified. [c] The reaction was done at 10–15 °C by suspending the aromatic compound in about 80 mL of Freon 113. [d] When the reaction was performed in $CHCl_3$ the yield dropped to 27%.

Strongly deactivated rings, however, had little effect on the equilibrium reaction between BrF_3 and bromine and consequently a very strong electrophilic bromine species was created which could cleanly react with the organic substrate without the use of any Friedel–Crafts catalyst. Furthermore, because of this equilibrium, the BrF concentration is always limited and the reaction can be carried at the very convenient temperature of around 0 °C. An additional important point is the fact that at higher temperatures the equilibrium tends toward the relatively unreactive BrF_3. This moderates the reaction rate to such a degree that, in spite of the large amount of heat evolved in reactions producing HF, there is often no need for a solvent.



The fact that the bromination results in *m*-bromo derivatives is a good indication of its ionic nature. Thus, nitrobenzene was reacted at about 0 °C with a 1:1.2 mixture of BrF_3/Br_2 and was instantaneously converted to *m*-bromonitrobenzene in 80% yield. Similar results were obtained with other monosubstituted aromatic derivatives (see Table I). The bromine in the BrF_3/Br_2 mixture is such a strong electrophile that it successfully reacts even with rings substituted with two electron-withdrawing groups. Thus, diethyl isophthalate was converted to diethyl 5-bromoisophthalate in 60% yield while diethyl phthalate gave two bromo derivatives, diethyl 3-bromo- and 4-bromophthalate, in 35% yield each. The real power of the reagent is best demonstrated with the most

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[1] Rozen, S.; Brand, M.; Lidor, R. *J. Org. Chem.* 1988, *53*, 5545.

[2] Kartashov, A. V.; Chuvatkin, N. N.; Boguslavskaya, L. S. *Zh. Org. Khim.* 1988, *24*, 2522.

[3] Boguslavskaya, L. S.; Kartashov, A. V.; Chuvatkin, N. N. *Zh. Org. Khim.* 1989, *25*, 2029. For related papers on this subject see also: Rozen, S.; Gal, C. *J. Org. Chem.* 1987, *52*, 2769 and 4928.

[4] This is a well-known equation. For the original work on it see: Steunenberg, R. K.; Vogel, R. C.; Fischer, J. *J. Am. Chem. Soc.* 1957, *79*, 1320.

0022-3263/93/1958-0239$04.00/0

deactivated 1,3-dinitrobenzene which was rapidly converted to the desired 5-bromo-1,3-dinitrobenzene in 65% yield.[5]

With compounds which melt above 10 °C, a small amount of an inert solvent such as Freon 113 was used. Thus, for example, 3-nitroacetophenone was successfully brominated to give 3-bromo-5-nitroacetophenone in 85% yield. Although, as mentioned above, activated aromatic compounds are not suitable for bromination by this method, compounds with a combination of electron-donating and electron-withdrawing groups can be brominated but in a somewhat lower yields. *p*-Nitrotoluene which was converted to 2-bromo-4-nitrotoluene in 40% yield can exemplify this category.

Experimental Section

^{1}H NMR spectra were recorded with a Bruker WH-360 spectrometer at 360 MHz with $CDCl_3$ as a solvent and Me_4Si as internal standard. Mass spectra were measured with a DuPont 21-491B spectrometer. IR spectra were recorded on a Perkin-Elmer 177 spectrometer.

Reagents. Aromatic compounds and solvents were of commercial grade and were not further purified. Although commercially available, we prepared our own BrF_3 by simply passing 1.7 mol of fluorine (25% in nitrogen) through 0.5 mol of bromine placed in a Teflon reactor at 0 °C. The pale yellow BrF_3 thus obtained has a mp of 7–9 °C[6] and can be stored in Teflon containers for long periods. It should be noted that at 0 °C the higher oxidation-state derivative BrF_5 will not form in any appreciable amounts.[7] BrF_3 is, however, a strong oxidizer and tends to react very exothermically with water and many organic solvents. The work should be conducted in a well-ventilated area and caution and common sense be exercised.

General Brominating Procedure. A mixture of 0.1 mol (5 mL) of BrF_3 and 0.12 mol (6.5 mL) of bromine (0.3 mol of active bromine) was added dropwise into a cooled (0 °C) flask containing ca. 0.5 mol of the aromatic substrate and equipped with a magnetic stirrer and condenser. The excess of the aromatic compound was to ensure monobromination only. The addition was carried out with vigorous stirring, keeping the temperature between 0 and 10 °C. It should be noted that two other modes of reaction could be employed with similar results: (a) adding the BrF_3 to a mixture of the organic substrate and bromine and (b) sweeping the mixture of the BrF_3/Br_2 into the cooled aromatic compound with a stream of nitrogen. After the addition was complete the crude reaction mixture was poured into a stirred, iced 5% sodium sulfite solution. The organic layer was separated, and the aqueous solution was twice extracted with 100 mL of CH_2Cl_2. The combined organic layer was washed with 5% sodium bicarbonate solution and then with water until neutral. The organic phase was dried over $MgSO_4$ and the solvent evaporated. The crude organic mixture was quantitatively analyzed by a GC internal standard program. The bromoaromatics were usually separated from the unreacted starting material by distillation under reduced pressure. The yields are based on the reacted aromatic derivatives, and the conversions were practically quantitative in the sense that 3 mol/equiv of an aromatic compound was consumed for every mol/equiv of BrF_3. The physical and spectral properties of all products completely matched those of authentic samples or those appearing in the literature.

Registry No. $C_6H_5NO_2$, 98-95-3; C_6H_5CN, 100-47-0; $C_6H_5CF_3$, 98-08-8; C_6H_5COOMe, 93-58-3; C_6H_5Cl, 108-90-7; 1,3-$(COOEt)_2C_6H_4$, 636-53-3; 1,2-$(COOEt)_2C_6H_4$, 84-66-2; 3-$NO_2C_6H_4COCH_3$, 121-89-1; 4-$NO_2C_6H_4COCH_3$, 100-19-6; 4-$NO_2C_6H_4CH_3$, 99-99-0; 1,4-$(COOMe)_2C_6H_4$, 120-61-6; 1,3-$(NO_2)_2C_6H_4$, 99-65-0; *m*-$BrC_6H_4NO_2$, 585-79-5; *m*-BrC_6H_4CN, 6952-59-6; *m*-$BrC_6H_rCF_3$, 401-78-5; *m*-BrC_6H_4COOMe, 618-89-3; *p*-BrC_6H_4Cl, 106-39-8; 3,5-$(COOEt)_2C_6H_3Br$, 127437-29-0; 2,3-$(COOEt)_2C_6H_3Br$, 127413-58-5; 3,4-$(COOEt)_2C_6H_3Br$, 38568-41-1; 3-Br-5-$NO_2C_6H_4COCH_3$, 127413-59-6; 2-Br-4-$NO_2C_6H_4COCH_3$, 90004-93-6; 2-Br-4-$NO_2C_6H_4CH_3$, 7745-93-9; 2,5-$(COOMe)_2C_6H_3Br$, 18643-86-2; 3,5-$(NO_2)_2C_6H_3Br$, 18242-39-2; BrF_3, 7787-71-5.

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(5) Previously, direct bromination has been achieved in moderate yield by using silver trifluoromethanesulfonate, bromine, and concentrated sulfuric acid for 16 h at 90 °C: Huthmacher, K.; Effenberger, F. *Synthesis* **1978**, 693.

(6) Meshzi, D. T. In *Fluorine—The First Hundred Years*; Banks, R. E., Sharp, D. W. A., Tatlow, J. C., Eds.; Elsevier Sequoia: Lausanne and New York, S. A., 1986; Chapter 10.

(7) Stein, L. *J. Am. Chem. Soc.* **1959**, *81*, 1269.