A Convenient New Method for the Bromination of Deactivated Aromatic Compounds

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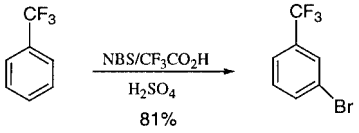
Abstract: Treatment of deactivated aromatic compounds with *N*-bromosuccinimide in trifluoroacetic acid solvent in the presence of sulfuric acid gave the corresponding monobromoaromatic compounds in good to excellent yields.

Key words: bromination, aromatic compounds

Bromoaromatics are highly useful synthetic intermediates, but ring bromination of strongly deactivated aromatics continues to pose synthetic problems. Among the reported methods for the bromination of deactivated aromatic compounds, many suffer from the use of hazardous reagents or harsh reaction conditions.[1,2] Thus, reagents which utilize *N*-bromosuccinimide (NBS) or the analogous 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) as the source of electrophilic bromine have emerged as being among the most useful for carrying out such difficult reactions.[3-7]

The first significant report was that of Lambert,[4] who, in a limited study, used NBS in an aqueous H_2SO_4 medium to brominate nitrobenzene. In a much more thorough and useful investigation, Eguchi used DBDMH with CH_3SO_3H, CF_3SO_3H, or H_2SO_4 in CH_2Cl_2 or $CHCl_3$ as solvent to successfully brominate a number of electron-deficient aromatics, including nitrobenzene, methyl benzoate and trifluoromethylbenzene.[5] However, more highly deactivated aromatics than these, such as *m*-dinitrobenzene, could not be brominated under such conditions. Schlosser, with a specific interest in brominating the highly unreactive 1,3-bis(trifluoromethyl)benzene, found that DBDMH in concentrated H_2SO_4 or CF_3SO_3H (without CH_2Cl_2 solvent) did that job nicely.[6]

Though all the reported methods based on NBS or DBDMH work well for the active and moderately deactivated aromatic compounds, they can not be applied to very strongly deactivated aromatic compounds, such as 1,3-dinitrobenzene. Our goal was to find bromination conditions that would be *generally* useful for deactivated benzenes, but most specifically, would be useful for brominating trifluoromethyl-substituted benzenes without giving rise to significant hydrolysis.



At this time we wish to report that use of trifluoroacetic acid (TFA) as solvent, with NBS and catalytic H_2SO_4 as the active source of electrophilic bromine, seems to be an ideal medium for bromination of deactivated aromatic compounds. For example, treatment of trifluoromethylbenzene with 1.5 equivalents of NBS in the presence of H_2SO_4 in TFA at room temperature gave *m*-bromo(trifluoromethyl)-benzene in good yield, with the efficiency of the reaction being dependent upon the concentration of sulfuric acid, as shown in Table 1. Without sulfuric acid the reaction does not occur, but if the ratio (V/V) of H_2SO_4 to TFA gets too high, (i.e., 0.4), hydrolysis of the trifluoromethyl group begins to be observed (Entry 4 of Table 1). Maintaining a ratio of 0.3 allows a good conversion, with little, if any, benzoic acid being formed.

Table 1 Effect of the ratio of H_2SO_4 to TFA (v/v) on the bromination of (trifluoromethyl)benzene at 26 °C.

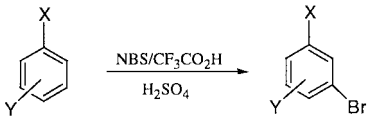
H_2SO_4/TFA(v/v)	Time(h)	Yield (%)[a]
0	48	0
0.2	48	62
0.3	48	81
0.4	38	91[b]

[a] by ^{19}F NMR; [b] Benzoic acid was detected by ^{1}H NMR

Brominations of other deactivated aromatics were found to proceed with similar success, with the results being given in Table 2. Even the very strongly deactivated aromatic compound, 1,3-dinitrobenzene, which was not able to be brominated under Eguchi conditions,[5] when subjected to our reaction conditions at slightly higher temperature (45 °C) for 48 h, gave the 5-brominated product in moderate (45%) yield.[8] As expected, relatively reactive aromatic compounds such as benzene reacted very rapidly with NBS/TFA/H_2SO_4 at room temperature. The reaction was complete in 2 h, giving bromobenzene in high yield (91%).

In our study, trifluoroacetic acid was found to be the most effective solvent of those examined, better than CH_2Cl_2, CH_3CO_2H, or H_2O, and it was the only one of this group

of solvents which allowed bromination of the least reactive substrates. Whereas Schlosser found pure H_2SO_4 to be an effective solvent for bromination of *m-bis* (trifluoromethyl)benzene,[6] we found that use of such conditions for the more hydrolytically-reactive (trifluoromethyl)benzene led to considerable hydrolysis of the trifluoromethyl group.



X = CF_3, NO_2, CO_2H, CHO, or H
Y = H, *p*-Cl, *p*-CF_3, *m*-CF_3, or *m*-NO_2

Table 2 Reactions of aromatic compounds with NBS/TFA/H_2SO_4[a]

Substrate	H_2SO_4/TFA (v/v)	t (hr)	Yield (%)[b]	bp, °C, (lit)
m-$(CF_3)_2C_6H_4$	0.4	51	84	152-153 (153-154)[6]
p-$(CF_3)_2C_6H_4$	0.1	48	62[c]	153-155 (161-162)[2]
p-$ClC_6H_4CF_3$	0.2	44	86	100-102/55mm (190-191)[2]
m-$(NO_2)_2C_6H_4$	0.4	48	45[d]	mp, 74-75 (75-76)[8]
$C_6H_5CF_3$	0.3	48	81	150-152 (151-153)[5]
$C_6H_5NO_2$	0.1	24	88	mp, 53-55 (53-54)[5]
$C_6H_5CO_2H$	0.2	44	78	mp, 154-156 (155)[9]
C_6H_5CHO	0.2	42	84	120-123/40mm (233-236)[9]
C_6H_6	0.1	2	91	155-156 (156)[9]

[a] at 25 °C; [b] isolated yields, with conversion of starting material, >90%; purity of products, >98%; [c] 2,4-dibromo-1,4-*bis*-(trifluoromethyl)-benzene was formed in 5% yield; [d] reaction run at 45 °C.

The mechanism of the reaction was not investigated. However, it is likely that the active brominating agent is either the protonated NBS or CF_3CO_2Br.

In conclusion, a mild and efficient general procedure for bromination of aromatics has been developed which because of its experimental simplicity, its selectivity, and its ability to be applied to highly deactivated substrates, should find wide application.

General Experimental Procedure:

Into a 250 mL round-bottomed flask, equipped with overhead stirrer, was placed 50 mL trifluoroacetic acid, 100 mmol aromatic compound, and an appropriate amount of sulfuric acid (98%). The mixture was stirred vigorously, and 150 mmol of NBS was added in portions over an 8 hour period. After the appropriate reaction time (reaction monitored by ^{19}F NMR or ^{1}H NMR), the mixture was poured into 200 mL of ice water, the organic layer separated, and the aqueous layer extracted with CH_2Cl_2 (20 mL x 3). The combined organic layers were washed with brine and dried over $CaCl_2$. After the CH_2Cl_2 was evaporated, distillation or recrystallization gave the desired product with the yields given in Tables 1 and 2.

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