The Direct Trifluoromethylation of Aryl Chlorides using Burton's Reagent

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The copper–dibromodifluoromethane–*N,N*-dimethylacetamide reaction system trifluoromethylates electronically activated aryl chlorides possessing *ortho* groups capable of interacting with the metal.

The physiological activity of many trifluoromethylated aromatic compounds has resulted in considerable interest in the development of inexpensive and convenient synthetic routes to compounds of this type. Some of the problems of the classical methods of constructing the CF_3 moiety, such as the use of toxic reagents and harsh conditions, can now be overcome by the use of '$CuCF_3$' which is normally generated *in situ* by the reaction of copper metal or a copper(I) salt and a source of the trifluoromethyl group.[1,2] The most elegant of the '$CuCF_3$' routes is that developed by Burton which involves the use of relatively inexpensive difluorodihalomethanes as the fluorine source.[2] The major drawback remaining with such methods is the use of aryl iodides as the starting materials since they are expensive and often difficult to obtain with the required substituents. Here we report our results from a preliminary investigation of the reactions of copper metal–dibromodifluoromethane–*N,N*-dimethylacetamide ($Cu–CF_2Br_2$–DMAc) reaction system with a range of aryl chlorides.

Reaction of the highly electrophilic substrate chloro-2,4-dinitrobenzene with $Cu–CF_2Br_2$–DMAc at 100 °C in a nitrogen atmosphere gives 93% conversion into 2,4-dinitrobenzotrifluoride after 4 hours, with only a small amount of contamination by 2,4-dinitrobenzene. Other polar amide solvents can also be used, although these generally give less selective reactions (Table 1). The less electrophilic chloronitrobenzenes are significantly less reactive under these conditions and, more interestingly, reveal a large *ortho* group effect so that the order of reactivities towards trifluoromethylation is 2-chloronitrobenzene $\gg$ 4-chloronitrobenzene $>$ 3-chloronitrobenzene (Table 1). By studying the reactions of a range of 2-substituted aryl chlorides we discovered a clear dependence of the reactivity of the substrate on the nature of the *ortho* group. Thus, while the groups NO_2, CO_2R, COR, and ring nitrogen encourage trifluoromethylation, H, CN, CF_3, NH_2, OR, and SR do not. We interpret these results in terms of the relative ability of the *ortho* group to hold the copper species (presumably $CuCF_3$) in close proximity to the reaction site.[3] This *ortho* group effect can be usefully exploited

Table 1. Trifluoromethylation of aryl chlorides.[a]

Starting material	Reaction time/h	Major product	% Yield[b]	Minor product(s)	% Yield[b]
Chloro-2,4-dinitrobenzene	4	2,4-Dinitrobenzotrifluoride	93	1,3-Dinitrobenzene	2
Chloro-2,4-dinitrobenzene[c]	8	2,4-Dinitrobenzotrifluoride	88	1,3-Dinitrobenzene	2
Chloro-2,4-dinitrobenzene[d]	4	2,4-Dinitrobenzotrifluoride	83	1,3-Dinitrobenzene	15
Chloro-2,4-dinitrobenzene[e]	8	2,4-Dinitrobenzotrifluoride	93	1,3-Dinitrobenzene	4
Chloro-2,4-dinitrobenzene[f]	8	1,3-Dinitrobenzene[g]	97		
2-Chloronitrobenzene	8	2-Nitrobenzotrifluoride	59		
3-Chloronitrobenzene	8	—[g]			
4-Chloronitrobenzene	8	4-Nitrobenzotrifluoride	5	Nitroperfluoroalkylbenzenes[h]	1
Chloro-3,4-dinitrobenzene	8	3,4-Dinitrobenzotrifluoride	8	3,4-Dinitroperfluoroalkylbenzenes[h]	8
				Chloronitrobenzotrifluorides	9
4-Chloro-3,5-dinitrobenzotrifluoride	0.5	3,5-Dinitro-1,4-bis(trifluoromethyl)benzene	83	3,5-Dinitrobenzotrifluoride	15
Methyl 2-chlorobenzoate	8	Methyl 2-trifluoromethylbenzoate	17	Methyl 2-perfluoroalkylbenzoates[h]	17
2-Chloro-5-nitrobenzophenone	8	5-Nitro-2-trifluoromethylbenzophenone	47		
2-Chloropyridine	8	2-Trifluoromethylpyridine	13	2-Perfluoroalkylpyridines[h]	23
2-Chloro-5-nitropyridine	8	5-Nitro-2-trifluoromethylpyridine	48	5-Nitro-2-perfluoroalkylpyridines[h]	18
2-Chloropyrimidine	8	2-Trifluoromethylpyrimidine	46	2-Perfluoroalkylpyrimidines[h]	50

[a] Reactions were carried out at 100 °C in *N,N*-dimethylacetamide, unless stated otherwise; products were confirmed by mass and ^{19}F n.m.r. spectral data. [b] Determined by g.c. [c] *N,N*-Dimethylformamide as solvent. [d] *N*-Methylpyrollidone as solvent. [e] Dimethylpropylurea as solvent; 90 °C. [f] Dimethylsulphoxide as solvent. [g] No trifluoromethylation was observed. [h] Mostly C_2F_5 and C_3F_7 substituted products.

in, for example, the reaction of 2,3-dichloronitrobenzene which gives 6-chloro-2-nitrobenzotrifluoride in good yield with no contamination by the other isomer or the bis(trifluoromethylated) product. It should be noted, however, that the formation of higher perfluoroalkyl substituted products such as ArC_2F_5 is a problem in the reaction of the less activated substrates (Table 1).

Our results clearly show that a large number of aryl chlorides can indeed be considered as viable substrates for the preparation of benzotrifluorides. Reactions with $Cu-CF_2Br_2$–DMAc are likely to involve nucleophilic attack on the substrate by a $CuCF_3$-type species, with co-ordination of that species by non-labile groups *ortho* to the chlorine playing a vital role in controlling the rate and site of reaction.

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References

1 V. C. R. McLaughlin and J. Thrower, *Tetrahedron*, 1969, **25**, 5921; Y. Kobayashi and I. Kumadaki, *Tetrahedron Lett.*, 1969, 4095; Y. Kobayashi, K. Yamamoto, and I. Kumadaki, *ibid.*, 1979, 4071; K. Matsui, E. Tobita, M. Ando, and K. Kondo, *Chem. Lett.*, 1981, 1719.

2 D. M. Wiemers and D. J. Burton, *J. Am. Chem. Soc.*, 1986, **108**, 832.

3 J. Lindley, *Tetrahedron*, 1984, **40**, 1433.