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Bromodifluoromethylation of aromatic Grignard reagents with CF₂Br₂

ABSTRACT

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Organofluorine compounds have been widely utilized in the areas of medicinal chemistry, agricultural chemistry, and material science.¹ To enable facile access to these fluorinated compounds, recent researches focus on the development of introducing fluorine-containing functional groups with accompanying carbon—carbon bond formation. Among fluorinated functional

groups, the bromodifluoromethyl (CF₂Br) group is a versatile one because various bromodifluoromethylated aromatics have served as precursors of [¹⁸F]trifluoromethylated compounds for positron emission tomography (PET) imaging,² liquid crystal (LC) com-pounds containing a -CF₂OAr moiety,³ fluoroparacyclophanes,⁴ and fluorinated polymers (Scheme 1).⁵ In addition, the CF₂Br group can be regarded as an equivalent of trifluoromethyl $(CF_3)^2$ and difluoromethyl $(CHF_2)^6$ groups. To introduce the CF_2Br group via carbon–carbon bond formation, dibromodifluoromethane (CF₂Br₂) has been used as a source of the CF₂Br group and several bromodifluoromethylations of carbon nucleophiles, such as acetylides⁷ and enolates,^{6c,8} were reported. Furthermore, recently, several electrophilic bromodifluoromethylating reagents (⁺CF₂Br) have been developed by Xiao,⁹ Magnier,¹⁰ and Shibata,¹¹ and the reactions of acetylides and malonates with these S-(bromodifluoromethyl)diarylsulfonium salts and S-(bromodifluoromethyl)sulfoximines were demonstrated.



The bromodifluoromethylation of aromatic Grignard reagents having electron-withdrawing groups with

dibromodifluoromethane (CF₂Br₂) was developed. The reaction proceeded to give the corresponding (bro-

modifluoromethyl)benzene derivatives via a difluorocarbene-mediated mechanism.

Scheme 1. Bromodifluoromethylation and derivatization.

On the other hand, in terms of aromatic bromodifluoromethylations, only a few reactions using arylmetal reagents were reported. South et al. disclosed that treatment of the dianion of 2-trifluoroacetoamido-4-(trifluoromethyl)thiazole with CF₂Br₂ at -98 °C produced the corresponding 5-(bromodifluoromethyl)thiazole derivative.¹² They commented that this reaction is unusual because the reaction of 2-(trifluoromethyl)phenyllithium with CF₂Br₂ gave a quantitative yield of 1-bromo-2-(trifluoromethyl) benzene. In addition, as shown in Scheme 2, Matsui and co-workers reported that treatment of 2,6-difluorophenyllithium 1 with CF₂Br₂ below -70 °C produced 1-(bromodifluoromethyl)-2,6difluorobiphenyl derivative 2 and aryl bromide 3 with a ratio of 8:2.³ Although this method has been used in the LC compound synthesis, generally two fluorine atoms substituted at the C-2 and C-6 positions of **1** are required to proceed the reaction. To our best knowledge, these were the only two examples of the bromodifluoromethylation of arylmetal species with a ⁺CF₂Br equivalent. The substrates were limited and the generality of the reaction is





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Scheme 2. Aromatic bromodifluoromethylation by Matsui et al.³

unknown. As a part of our project on the development of new methods for the introduction of fluorine-containing functional groups into aromatic rings,¹³ we began to study the reaction of arylmetal species with CF_2Br_2 . Herein, we would like to report the bromodifluoromethylation of aromatic Grignard reagents possessing electron-withdrawing groups with CF_2Br_2 .

Initially, we attempted the reaction of 4-biphenylyllithium (4) with CF₂Br₂ as depicted in Scheme 3. Exposure of 4, prepared from 4-bromobiphenyl and *n*-BuLi, to CF_2Br_2 at -78 °C produced 4-bromobiphenyl (6), biphenyl (7), and difluorostilbene 8 in 39%, 16%, and 10% yields, respectively. Unfortunately, formation of the desired product **5** was not observed. As well as precedents,^{7,8} we speculated that aromatic bromodifluoromethylation of **1** proceeded via a carbene chain mechanism (Scheme 4, M = Li): (i) reaction of aryllithium A with CF₂Br₂ produced aryl bromide B and bromodifluoromethyl anion **C**, (ii) **C** was immediately decomposed to difluorocarbene \mathbf{D}^{14} with releasing LiBr, (iii) difluorocarbene **D** then combined with aryllithium **A**, affording aryldifluoromethyllithium **E**, and (iv) bromination of **E** with CF_2Br_2 yielded the targeted $ArCF_2$ Br **F** with the formation of **C**, which propagated the carbene chain reaction. In the case of the reaction of 4, the formation of 4-bromobiphenyl (6) (=B) as the major product indicated that the carbene insertion step (A-E) was slow. In addition, we regarded that difluorostilbene 8 (=H) was produced by dimerization of arylfluorocarbene **G**, which was generated through α -elimination of **E** accelerated by two fluorine atoms that destabilized the sp²-hybridized

benzyl carbanion.¹⁵ Since we thought that the key to success in the bromodifluoromethylation would be to enhance the stability of the intermediate **E**, which could accelerate the carbene insertion step (**A**–**E**) and prevent the decomposition (**E**–**G**).¹⁶ we then decided to explore the reaction of the arylmetal species **A** possessing electron-withdrawing groups on the aromatic ring with CF₂Br₂.

At first, the reaction of 4-cyanophenylmagnesium chloride (10a), prepared from 4-halobenzonitrile 9a and i-PrMgCl by Knochel's halogen-magnesium exchange reaction,¹⁷ with CF₂Br₂ was examined as shown in Table 1. Upon addition of a solution of CF₂Br₂ in THF to **10a** derived from 4-bromobenzonitrile (**9aa**) at -78 °C, the desired product **11a** was fortunately obtained in 27% GC yield concomitantly with the formation of **9aa** (7%) and benzonitrile 12 (15%) (entry 1). Next, the reverse addition of **10a** to CF₂Br₂ was examined, affording **11a** in the improved yield (37%) (entry 2). Interestingly, we observed the formation of a small amount of 4-(bromochlorofluoromethyl)benzonitrile (13) (7%).¹⁸⁻²⁰ When 4-iodobenzonitrile (**9ab**) was used in place of **9aa**, the yield (50%) was improved (entry 3). In the absence of LiCl, the reaction gave rise to the desired product 11a in 77% GC yield (45% isolated yield²¹) with a 3% yield of **13** (entry 4).²² We regarded that the decrease of the isolated yield was due to the volatility of 11a. While further investigations to improve the yield were carried out in several solvents, such as dioxane, DME, and diglyme (entries 5–7), THF gave the best result. Interestingly, the yield was diminished in the case of using 4-bromobenzonitrile



Scheme 3. Attempt of bromodifluoromethylation of 4-biphenylyllithium (4).



(M = Li or MgCl)

Scheme 4. Plausible reaction mechanism of the bromodifluoromethylation.

 Table 1

 Bromodifluoromethylation of aryl Grignard reagent 10a

		NC – 9aa: X: 9ab: X: CF ₂ Br ₂	$= \frac{1}{2} - X - \frac{1}{2} - X - \frac{1}{2}$ $= Br$ $= I$ (1.2 eq) $V_{T} \rightarrow N$	IGCI (1.06 er	q) → NC-√ 10 :F ₂ Br + NC-	→MgCl a			
		–78 °C	to rt, 8 h	11a	9aa 12: 13:	a: R = Br R = H R = CFClBr			
Entry	Х	LiCl (equiv)	Solvent	Method	Temp (°C)	Yield ^a (%)			
						11a	9aa	12	13
1	Br	2.4	THF	A ^b	-40 to rt	27	7	15	0
2	Br	2.4	THF	Bc	-40 to rt	37	9	3	7
3	Ι	2.4	THF	В	-40	50	13	3	7
4	Ι	0	THF	В	-40	77 (45) ^d	5	5	3
5	Ι	0	dioxane	В	rt	37	9	3	7
6	Ι	0	DME	В	-40	50	13	3	7
7	Ι	0	diglyme	В	-40	50	5	5	3
8	Br	0	THF	В	-40 to rt	30	8	13	2
9 ^e	Ι	0	THF	В	-40	50	10	7	3

^a Determined by GC analysis using undecane as an internal standard.

^b Method A: A solution of CF₂Br₂ in THF was added dropwise into the Grignard reagent.

^c Method B: The Grignard reagent was added dropwise into a solution of CF₂Br₂ in THF.

^d Isolated yield.

^e 2.4 equiv of CF₂Br₂ were used.

9aa (entry 8)²³ and increasing amount of CF_2Br_2 (2.4 equiv) did not improve the yield (entry 9). Unfortunately, the reactions using the corresponding arylzinc and arylcopper reagents did not proceed.

With the optimized reaction condition in hand, we next evaluated the substrate scope of this reaction by using several aryl Grignard reagents 10 having electron-withdrawing groups, prepared from the corresponding aryl halides 9, to obtain the (bromodifluoromethyl)benzene derivatives **11** as shown in Table 2.^{21,23} The reactions of *m*- and *o*-cvanophenyl Grignard reagents gave **11b** and **11c** in 41% and 71% isolated yields, respectively. In the case of the cyanophenyl Grignard reagents with halogen atoms, the desired products 11d-11f were obtained in 54-71% yields. In addition, p-cyanophenyl Grignard reagents with electron-donating groups, such as allyloxy and methoxy groups, also produced the corresponding bromodifluoromethyl products 11g-11h in 54% yields. Next, we examined aryl Grignard reagents 10 with other electron-withdrawing groups, such as methoxycarbonyl, pentafluorosulfanyl, and arylsulfonyl groups. These electron-withdrawing groups also worked to stabilize the intermediate aryldifluoromethyl anion, giving rise to 11i-11l in moderate yields (33-41%). While the yields were decreased to around 20% yields, the reactions of some trifluoromethylated aryl Grignard reagents with CF₂Br₂ also proceeded to give **11m–110**. In addition, polyhaloaryl compound 11p was obtained in moderate yield (39%) and 2-(trifluoromethyl)-5-pyridyl Grignard reagent produced a 29% yield of bromodifluoromethylated pyridine 11q. Unfortunately, the reactions of phenyl and 4-methoxyphenyl Grignard reagents with CF₂Br₂ gave no desired products (11r and 11s) and the corresponding bromobenzene derivatives were mainly produced. At the moment, we conclude that it is essential to use aromatic Grignard reagents with electron-withdrawing groups in this reaction. The cyano group is the most preferred one with the following order: -CN (0.66, 0.18) > -SO₂Ar (0.69, 0.12) > -CO₂Et $(0.45, 0.16) \approx -SF_5$ (0.68, 0.07) > -CF₃ (0.54, 0.09). The values in parentheses indicate Hammett σ_p and σ_R values, respectively,²⁴ and we regarded the resonance effect of the substituent may facilitate the reaction. We regarded that this bromodifluoromethylation also proceeded via a carbene-mediated mechanism as described in Scheme 4 (M = MgCl), in which the intermediate aryl-difluoromethyl anion **E** was stabilized by an electron-withdrawing group (=FG) through inductive and resonance effects, eventually affording the desired product **F**. Generally, (bromodifluoromethyl)benzene derivatives were prepared by radical bromination of α, α, α -trifluorotoluenes ^{2a,b,4a,25} and defluorobromination of α, α, α -trifluorotoluenes by BBr₃,²⁶ however, these reactions required harsh reaction conditions and/or hazardous reagents. Compared with these reactions, our developed method is a simple way to access (bromodifluoromethyl)benzene derivatives.

Since the bromodifluoromethyl $(-CF_2Br)$ group is a potential precursor of trifluoromethyl $(-CF_3)$, difluoromethyl $(-CHF_2)$, and (aryloxy)difluoromethyl $(-CF_2OAr)$ groups, we then examined to derivatize the bromodifluoromethyl compound **11k** as shown in Scheme 5. Thus, fluorination of **11k** by exposure to tetra-*n*-butyl-ammonium fluoride under heating in toluene provided (trifluoromethyl)benzene derivative **14** in 80%. Reduction of **11k** with tri-*n*-butyltin hydride offered difluoromethyl compound **15** in 90%. Additionally, heating of **11k** in the presence of *p*-nitrophenol and K₂CO₃ in DMF at 80 °C afforded a 65% yield of difluoromethyl ether **16**.

In summary, we have developed the novel aromatic bromodifluoromethylation of aryl Grignard reagents containing electronwithdrawing groups, such as -CN, $-CO_2Me$, $-SF_5$, $-SO_2Ar$, $-CF_3$, and halides, with CF_2Br_2 . We assumed the reaction proceeded via a carbene chain mechanism. The resulting bromodifluoromethyl compounds were successfully converted to the corresponding trifluoromethyl, difluoromethyl, and (aryloxy)difluoromethyl derivatives. Further studies on the mechanism and scope of this aromatic bromodifluoromethylation are currently under investigation in our laboratory.



^a Isolated yield.

^bAryl iodide **9** was used for the reaction.

^cAryl bromide **9** was used for the reaction.

 d 1.5 equiv of CF₂Br₂ were used.

^eMg (1.2 equiv) was used instead of *i*-PrMgCl.



Scheme 5. Derivatization of 11k.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.10.082.

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- We speculated that 4-(bromochlorofluoromethyl)benzonitrile (13) was produced from arylfluorocarbene G. The intermediate G was trapped by Cl⁻ from LiCl and/or MgBrCl and the resulting ArCFCl-MgCl was brominated with CF₂Br₂ to give 13.
- For a recent example of the synthesis of bromochlorofluoromethyl compounds, see: Zhao, Y.; Gao, B.; Hu, J. J. Am. Chem. Soc. 2012, 134, 5790.
- 20. Further investigation to obtain this compound selectively is in progress in our laboratory and the results will be disclosed in due course.
- 21. All reactions gave a mixture of the desired product (Ar-CF₂Br) and the corresponding bromobenzene (Ar-Br), benzene (Ar-H), and bromochloro-fluoromethylbenzene (Ar-CFClBr) derivatives. Owing to the difficulty of separation of this mixture by silica gel column chromatography, the desired product was purified by recycle GPC to remove the side products.
- 22. A negligible amount of 4-(2-bromo-1,1,2,2-tetrafluoroethyl)benzonitrile was detected by GC (<1%). We regarded that this side product was produced from the intermediate **E**, which reacted with difluorocarbene **D** to afford aryltetra-fluoroethyl anion (ArCF₂CF₂-M) and the resulting anion was brominated with CF₂Br₂.
- 23. Although using 4-bromobenzonitrile in place of the iodide diminished the yield of the reaction (entry 8, Table 1), some of the reactions in Table 2 were carried out from bromobenzene derivatives due to commercial availability. Contrary to the result of 4-bromobenzonitrile, they proceeded as well as from other iodobenzene derivatives.
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