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Novel synthetic approaches to CHBrFI, CHClFI and CHBrClI

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Abstract—Three new facile methods for the preparations of racemic mixtures of CHBrFI, CHClFI and CHBrClI are described. Mercuric fluoride was found to be an effective fluorinating agent in fluorinations of CHI_2Br (**6**) and CHI_2Cl (**8**) to yield CHBrFI, CHClFI, respectively. Chlorination of CHI_2Br (**6**) by using antimony pentachloride as a chlorinating agent, afforded CHBrClI in convenient and mild condition.

1. Introduction

Chiral halomethanes are the smallest chiral molecules[1] and have general formula (CWXYZ) where W, X, Y, Z can be H, F, Cl, Br, I. All such molecules lack any symmetry i.e. belong to the C_1 point group. There are five molecules **1**–**5** (five enantiomeric pairs) belonging to the group (Fig. 1). Since the experimental determination of the maximum optical rotation and absolute configuration of the halomethanes are of great interest in the context of modern theories of optical activity,[2] numerous attempts to prepare and isolate enantiomers of the halomethanes have been made to date. One of them (CHBrClF) (**4**) has been the subject of various investigations pertaining to important chemical aspects of chirality,[3] halomethanes **1**–**3** have also been studied by UV photoelectron spectroscopy as possible substrates for 'chiral photoionization'.[4] Despite these explorations, little is known about the other four halomethanes, arising mainly from the lack of facile synthetic approaches. Although Haszeldine[5] reported the syntheses of CHBrFI (**1**) and CHClFI (**2**) via classical Hunsdiecker reaction and Hine[6] reported the preparation of CHBrClI (**3**) by the treatment of $CHBr_2Cl$ with sodium iodide (Scheme 1), limitations associated with these syntheses and sample purification remained. As shown in Scheme 1, the reported methods for the preparations of CHBrFI (**1**) and CHClFI (**2**) involved inconvenient and expensive preparations of silver bromofluoroacetate and silver chlorofluoroacetate, and required harsh conditions, such as high temperature, high vacuum, anhydrous environment etc. Also, the reported synthetic approach to CHBrClI (**3**) involved tedious purification procedures. Consequently, our interest in the halomethanes has encouraged us to search for more convenient synthetic approaches for their preparation and the approaches are reported in this paper.

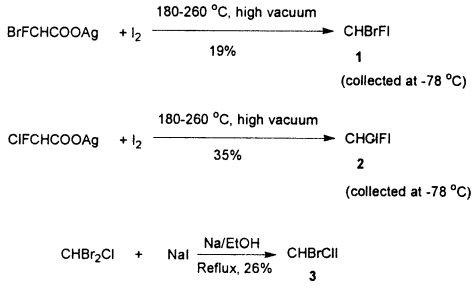
CHBrFI **1** CHClFI **2** CHBrClI **3**

CHBrClF **4** CBrClFI **5**

Figure 1. The formulae of halomethanes of type CWXYZ (X, Y, W, Z=H, F, Cl, Br, I).

2. Results and discussion

Various fluorinating agents have been developed for the purpose of replacing halogens by fluorine in organic halides.[7] The direct replacement of a bromine or iodine atom by reaction with mercury(II) or silver(I) fluoride has frequently been the procedure of choice for such syntheses, since these reactions can proceed under mild conditions. Furthermore, it has been found that mercuric fluoride can be used instead of silver fluoride in most cases where these silver salts could be used; the yields are considerably higher, most reactions take place smoothly at room temperature and side reactions are minimized or absent.[7c] In particular, the fluorinating agent has been well developed for the efficient method of preparation of CHBrClF (**4**).[3d] Very stable bromodiiodomethane, CHI_2Br (**6**),[8] makes it possible



Scheme 1. The reported methods for the preparation of halomethanes **1**–**3**.

Keywords: halomethanes; fluorination; chlorination.
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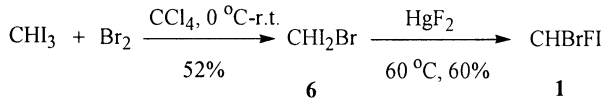
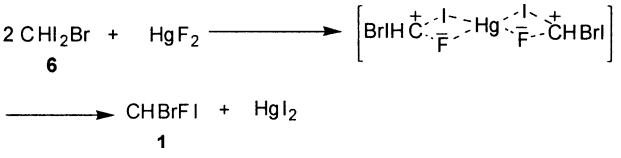


Scheme 2.

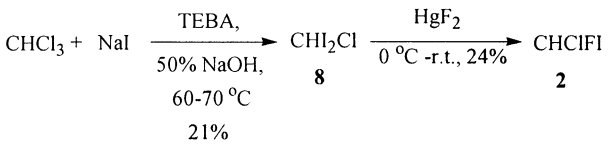
to explore a new synthetic approach to CHBrFI (**1**) by using mercuric fluoride as the fluorinating agent to replace one of the iodine atoms in the molecule. Our initial study verified that **6** reacts smoothly with mercuric fluoride in dry 1,4-dichlorobenzene at room temperature and the ^{13}C NMR spectrum clearly showed the formation of crude **1**.[9] Since the melting point of **6** is 60°C,[8] it is possible to treat it with mercuric fluoride directly without any extra solvent when the reaction temperature is up to 60°C. Hence, the neat reaction of halomethane **6** with 0.5 equiv. of mercuric fluoride at 60°C was examined and the expected CHBrFI (**1**) was successfully prepared in 60% yield after convenient purification (Scheme 2). In an effort to optimize the reaction conditions, we have further discovered that the amount of mercuric fluoride used is very critical to the reaction. When a stoichiometric amount of mercuric fluoride was added, almost no conversion of **6** to **1** was observed and only a solid mixture was obtained. This may be due to further conversion of **1** to a gaseous CHF_2Br in the presence of excess mercuric fluoride. In addition, when the reaction time was extended up to 2 h or the reaction temperature was over 70°C, we observed that the yield fell drastically and some liquids with higher boiling point were separated. Presumably the thermal instability of **1** causes some of it to decompose under more stringent conditions.[5] Therefore, both longer reaction time and higher reaction temperature proved to be unfavorable.

Scheme 3 illustrates a plausible mechanism for the reaction.[7c] The initial step is the formation of a halometalloate complex, then the C–F bond-forming step in the reaction can be achieved by the intermolecular transfer of fluoride from the complex to the carbonium ion center to afford the corresponding halomethane **1**. Since only one iodine atom in substrate **6** is involved in the reaction (on the basis of the proposed mechanism) and only halomethane **1** is the expected product, the use of 0.5 equiv. of mercuric fluoride was expected to be required, this was consistent with the actual results observed.

Our efforts to explore a more convenient and milder synthetic approach to another halomethane **2** were initially focused on chlorination of diiodofluoromethane, CHI_2F (**7**),[10] by using suitable chlorinating agents to replace the iodine atom in **7**. However, the efforts proved unsuccessful due to several drawbacks related to the properties of **2**. The main problem was the choice of a suitable reaction solvent, which is always needed for the chlorination reaction,



Scheme 3.

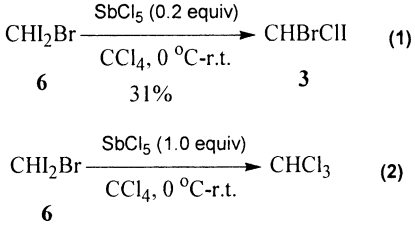


Scheme 4.

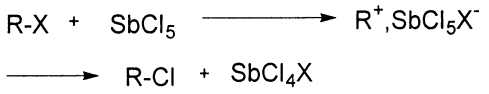
because of its low boiling point (ca. 76°C) and high volatility.[5] Therefore, the neat reaction of diiodochloromethane, CHI_2Cl (**8**),[11] with mercuric fluoride was attempted as an alternative strategy for the preparation of **2**. Although **8** is unstable towards air and light, fresh halomethane **8** can still be utilized as the starting material as indicated by ^1H NMR spectroscopy analysis. Furthermore, it makes it possible to perform fluorination of **8** (by HgF_2) at room temperature, since **8** is a liquid. Therefore, halomethane **8** was treated overnight with 0.5 equiv. of mercuric fluoride at room temperature in a flask with a Teflon stopcock and the reaction afforded the required **2** in 24% yield after distillation (Scheme 4). Because of the instability of **8** and the physical properties of **2**, a higher reaction temperature is not suitable for increasing the yield of **2**. Furthermore, the increase of the amount of mercuric fluoride from 0.5 to 0.7 equiv. only caused a slight increase of the product yield. Although the increase implied that the amount of mercuric fluoride used was not very critical for the conversion, the minimum amount used (0.5 equiv.) is still a good choice, considering that HgF_2 is highly toxic.

In view of the use of the same fluorinating agent and similar substrate (as for the preparation of **1**), a similar mechanism can be suggested for the fluorination of **8** (Scheme 3). Furthermore, compared with Haszeldine's method,[5] this approach does not involve any harsh conditions, can be performed even at room temperature, utilizes conveniently available and inexpensive halomethane **8** as the starting material, and affords halomethane **2** in comparable yield. Therefore, our approach to the preparation of **2** appears superior to the earlier method.

Although chlorination of **7** has proved to be an unsuccessful strategy for obtaining **2**, our interest in chlorination reactions of methyl halides prompted us to develop the synthetic strategy for the other halomethanes. The high boiling point of halomethane CHBrClI (**3**) makes it possible to utilize it to replace Hine's method,[6] since the properties of **3** are such that the reaction solvent can be used. Antimony pentachloride is an efficient and inexpensive chlorinating agent, used successfully in various chlorination reactions of aliphatic halides under mild conditions.[12] Hence, we tried to utilize halomethane **6** and antimony pentachloride as



Scheme 5.



Scheme 6.

potential reactants to explore the preparation of **3**. The reaction of **6** with 0.2 equiv. of 1.0 M solution of antimony pentachloride in CH_2Cl_2 was performed in anhydrous CCl_4 at room temperature, overnight under nitrogen and the expected halomethane **3** was generated in 31% yield after distillation under reduced pressure (Scheme 5, Eq. (1)). We further discovered that the amount of antimony pentachloride used is also critical in this reaction. When the amount of antimony pentachloride was increased up to 1.0 equiv., no residues remained in the flask after work-up. This observation implies that a complete conversion of **6** to chloroform may occur under these conditions (Scheme 5, Eq. (2)). A general chlorination mechanism by antimony pentachloride as suggested by Kagan (Scheme 6)[12] may rationalize the interpretation of both reactions. When 0.2 equiv. of antimony pentachloride was added, only one iodine atom in **6** was subjected to chlorine–iodine exchange with antimony pentachloride and the corresponding halomethane **3** was produced. However, when 1.0 equiv. of antimony pentachloride was loaded, all halogen atoms in **6** were involved in chlorine–halogen exchange with antimony pentachloride and the final product, chloroform, was formed and then easily removed during work-up.

Besides antimony pentachloride, other chlorinating agents, such as mercuric chloride, zinc chloride and iron(III) chloride were also tried, but proved unsuccessful in the reaction. Although mercuric chloride reacted with halomethane **6** to afford halomethane **3**, the poor yield and low purity of **3** precluded its use as a suitable reagent. Furthermore, zinc chloride and iron(III) chloride did not show any reactivity even at longer reaction time and higher reaction temperature. In comparison with Hine's method,[6] the reaction is mild and affords good yield. Thus, we can conclude that our novel approach to halomethane **3** using antimony pentachloride is superior to the previously used method.

3. Conclusion

In conclusion, three new facile methods of fluorination and chlorination for the interconversion of an iodine atom in methyl halides into a fluorine or a chlorine atom to yield the corresponding halomethanes **1**–**3** have shown synthetic advantages due to their mild and convenient conditions. This represents an important 'supply route' for the study of important physical and chemical aspects of chirality on the example of halomethanes. Our effort to synthesize the remaining halomethane, CBrClFI (**5**), is in progress.

4. Experimental

4.1. General

Unless otherwise specified, all materials were obtained from commercial suppliers and used without further purification. Mass spectra were recorded in electron ionization (EI) mode. FT-IR spectra were recorded as either neat film or KBr salt plate. ^{1}H NMR spectra were recorded at 300 MHz in $CDCl_3$ and ^{13}C NMR spectra were obtained at 75 MHz in $CDCl_3$, ^{19}F NMR spectrum was obtained at 282 MHz in $CDCl_3$ and chemical shifts were referenced internally with trifluoroacetic acid (TFA) (δ 0.00 ppm) as the internal standard. Dibromofluoromethane was prepared as reported previously.[13]

4.1.1. Bromodiiodomethane (6).[8] Iodoform (39.4 g, 100 mmol) and CCl_4 (70 mL) were charged into a 250 mL round-bottom flask at 0°C. A solution of bromine (3.75 mL, 73.5 mmol) in CCl_4 (50 mL) was added dropwise at 0°C during a period of 1 h. After addition, the resulting mixture was allowed to warm up to room temperature and stirred overnight. Saturated Na_2SO_3 solution was added to remove iodine formed and unreacted bromine. The CCl_4 layer was separated, washed with brine and dried over Na_2SO_4. After removal of solvent, the light purple residue was recrystallized from hexane to afford **6** as a yellow plate solid (18.2 g, 52%). Mp 59°C [Lit.[8] 60°C], ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.74 (s); ^{13}C NMR (75 MHz, $CDCl_3$) δ −99.58; MS(EI): *m/z* (relative intensity) 348 (M^++2, 67), 346 (M^+, 66), 219 (100), 140 (59), 94 (46); HRMS(EI): calcd for $CHBrI_2$ 345.7349, found 345.7351; IR (KBr): 1114, 1064, 617, 591, 574 cm^{-1}.

4.1.2. Diiodofluoromethane (7).[†] Sodium iodide (75 g, 0.5 mol) and dibromofluoromethane[13] (19.2 g, 0.1 mol) were charged into a 250 mL Teflon stopcocked flask under nitrogen, anhydrous acetone (100 mL) was added. After closing the flask tightly, the mixture was heated to 100–110°C for 8 days with stirring. After cooling down, the resultants were distilled under high vacuum with dry-ice condenser. The resulting liquid was concentrated under water aspirator at room temperature to remove acetone and the residue redistilled under reduced pressure to afford **7** as an amber liquid (7.0 g, 25%). Bp 62–64°C/30 mmHg, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (d, J_{H-F}=48.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.33 (d, J_{C-F}=318.5 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) (TFA) δ −26.38 (t, J_{F-C}= 30.5 Hz, J_{F-H}=15.2 Hz); MS(EI): *m/z* (relative intensity) 286 (M^+, 79), 267 (8), 159 (100), 140 (48); HRMS(EI): calcd for CHI_2F 285.8149, found 285.8150; IR (neat): 1682, 1615, 1090, 1054, 1017, 624 cm^{-1}.

4.1.3. Chlorodiiodomethane (8).[11] Chloroform (40 mL, 0.5 mol), triethylbenzylammonium chloride (TEBA) (2.0 g, 8.8 mmol), 50% of NaOH solution (40 mL) and the solution of NaI (200 g, 1.33 mol) in water (88 mL) were charged into a 250 mL round-bottom flask. The resulting mixture was heated to 60–70°C for 24 h. After cooling down, the mixture was poured into water (560 mL) and extracted with CH_2Cl_2 (100 mL×4). The CH_2Cl_2 layer was separated, washed with saturated Na_2SO_3 solution, dried over Na_2SO_4, concentrated under reduced pressure to give deep red liquid and redistilled under water aspirator to give **8** (31.0 g, 21%) as a light sensitive liquid. Bp 106–108°C/

[†] The synthesis of diiodofluoromethane was previously reported,[10] but we prepared the compound by the modified procedure as described herein.

30 mmHg [Lit.[11] bp 81°C/13 mmHg], ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.19 (s); ^{13}C NMR (75 MHz, $CDCl_3$) δ −67.78; MS(EI): *m/z* (relative intensity) 302 (M^+, 63), 267 (25), 175 (100), 140 (25), 48 (36); HRMS(EI): calcd for $CHCl_2I$ 301.7854, found 301.7849; IR (neat): 1163, 1105, 1069, 720 cm^{-1}.

4.1.4. Bromofluoroiodomethane (1). Dry bromodiiodomethane (**6**)[8] (8.7 g, 25 mmol) and mercuric fluoride (3.0 g, 12.5 mmol) were charged into a 50 mL Teflon stopcock flask under nitrogen. The mixture was continuously mixed with stirring and slowly heated to 60°C for 1 h. After cooling down, the resultants were distilled under high vacuum with dry-ice condenser to give a light sensitive liquid, redistilled under water aspirator to give **1** as a light-sensitive liquid (3.61 g, 60%). Bp 36–38°C/30 mmHg [Lit.[5] bp 35°C/70 mmHg], ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, J_{H-F}=48.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.55 (d, J_{C-F}=316.1 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) (TFA) δ −15.60 (d, J_{F-H}=53.3 Hz); MS(EI): *m/z* (relative intensity) 240 (M^++2, 44), 238 (M^+, 44), 159 (38), 113 (100), 111 (100); HRMS(EI): calcd for CHBrFI 237.8289, found 237.8287; IR (neat): 1132, 1044, 909, 735, 673 cm^{-1}.

4.1.5. Chlorofluoroiodomethane (2). The fresh chlorodiiodomethane (**8**)[11] (25.4 g, 84 mmol) was charged into a 250 mL Teflon stopcocked flask under nitrogen. With stirring, mercuric fluoride (10.0 g, 42 mmol) was added in small portions at 0°C under nitrogen. After addition, the resulting mixture was allowed to warm up to the room temperature and stirred for 36 h. The resultants were distilled under high vacuum with dry-ice condenser to give a light sensitive liquid, redistilled under nitrogen to give **2** as a light sensitive liquid (3.85 g, 24%). Bp 74–76°C [Lit.[5] bp 35°C/150 mmHg], ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, J_{H-F}=50.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.04 (d, J_{C-F}=306.2 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) (TFA) δ −11.04 (d, J_{F-H}=53.3 Hz); MS(EI): *m/z* (relative intensity) 194 (M^+, 43), 159 (18), 67 (100), 48 (9); HRMS(EI): calcd for CHClFI 193.8794, found 193.8798; IR (neat): 909, 735, 651 cm^{-1}.

4.1.6. Bromochloroiodomethane (3). Bromodiiodomethane (**6**)[8] (10.41 g, 30 mmol) was dissolved into anhydrous CCl_4 (50 mL) under nitrogen. At 0°C, 1.0 M solution of antimony pentachloride in CH_2Cl_2 (6 mL) was added via syringe under nitrogen. The resulting mixture was allowed to warm up to the room temperature and stirred overnight. Saturated Na_2SO_3 solution was added and the organic phase separated, dried over Na_2SO_4, concentrated under water aspirator to give a light sensitive liquid, redistilled under reduced pressure to afford **3** as a light sensitive liquid (2.34 g, 31%). Bp 88–90°C/30 mmHg [Lit.[6] bp 68–69°C/30 mmHg], ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.71 (s); ^{13}C NMR (75 MHz, $CDCl_3$) δ −15.43; MS(EI): *m/z* (relative intensity) 256 (M^++2, 20), 254 (16), 175 (17), 127 (100), 48 (14); HRMS(EI): calcd for CHBrClI 253.7995, found 253.7999; IR (neat): 1179, 1106, 785, 731, 629 cm^{-1}.

Acknowledgements

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