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Synthetic routes for a variety of halogenated (chiral) acetic acids from diethyl malonate[†]

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Chiral halomethane is the smallest stable molecule with a single asymmetric C-atom and halogenated acetic acids often serve as precursors. We focus on a synthetic route to synthesise chiral halogenated acetic acids with F, Cl, Br, and H/D isotopic substitution at the α -C-atom starting from diethyl malonate. This reactant is easily available, cheap and allows the obtainment of target acids in a few reaction steps with great versatility. Among all of the possible fully halogenated acetic acids (more than one hundred, which are, in principle, accessible by this route), there are only a small number of chiral halogenated acetic acids, which have been synthesized following the devised synthetic route.

Introduction

Small chiral molecules are excellent prototype candidates for the investigation of molecular parity violation,^{1,2} the determination of absolute configurations by new direct methods based on Coulomb explosion imaging,^{3–6} and the study of frequency dependent chiroptical properties.^{7,8} Due to the small number of atoms, they are also well suited to high-quality *ab initio* calculations^{9–12} that are relevant for a detailed understanding of the spectroscopic investigations of chiral molecules.^{13–15}

The synthesis of chiral acetic acid with all three hydrogen isotopes at the chiral C-atom and known handedness was truly pioneering work for the investigation of enzyme reaction mechanisms back in 1969.^{16–18} Here we focus on chiral halogenated acetic acids,¹⁹ CXYZCOOH, which are of general interest in the fields mentioned above. They serve as precursors to halomethanes, specifically CHBrClF,^{20–23} CHBrFI,²⁴ and isotopically chiral CHDXY.^{25–28} CHBrClF (7) itself has been subject to very early attempts to measure parity violation effects in molecules.²⁹ Since the prediction and experimental verification of the weak interaction in particle physics in around 1956/57,^{30,31} it became immediately clear that this interaction also has consequences in chemistry: for an isolated enantiomer, racemization following $R = S$ leads to a tiny heat of reaction, $\Delta_r H^\circ$, in the order of 10^{-15} kJ mol^{−1} (ref. 32 and 33) which can be related to the parity violating energy difference, $\Delta_{\text{pv}} E$, between both enantiomers according to $\Delta_{\text{pv}} E \approx \Delta_r H^\circ$, thus leading to slightly

different absorption spectra of isolated *R* and *S* molecules. Attempts to measure these effects have failed until today,^{32–34} but molecular parity violation is still an active field of research.

The synthesis of these halomethanes usually starts from perhalogenated ethene (see Scheme 1).^{21,23} This reactant is not very well suited for the synthesis of a large variety of halogenated acetic acids since it has a low boiling point and is subject to producing undesirable byproducts. Furthermore, due to the CFC(chlorofluorocarbon)-ban in 1989, its commercial availability is very limited. We therefore examined a synthetic pathway starting from an easily available diethyl malonate.^{35–37} We explored the reaction scheme (Scheme 2) for the synthesis of a whole series of halogenated chiral (and also achiral) acetic acids with high yields and purity.³⁸ Some of these lead directly to the corresponding chiral halomethane upon decarboxylation.^{39,40}

Results and discussion

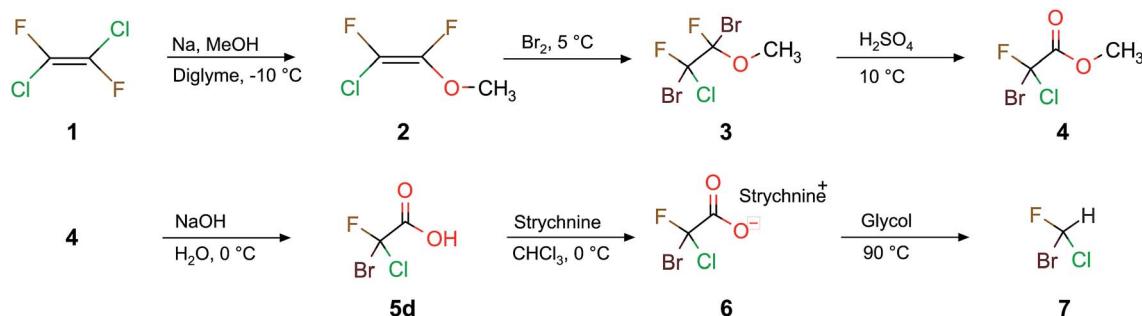
First we focus on CHBrClF (7) and its corresponding acetic acid (5d). A complete multistep synthesis for 7 was described by Doyle and Vogl^{22,39} and optimized by Beil *et al.*²¹ a few years later. Both research groups^{21,22,39} used the same experimental procedure as shown in Scheme 1 but instead of using 1,2-dichloro-1,2-difluoroethylene (1) they started with chlorotrifluoroethylene with different corresponding reaction conditions for some steps. Our modified synthetic route (Scheme 1) has some advantages compared to the past approaches that use chlorotrifluoroethylene as the starting material, namely 1 has a higher boiling point of about 19 °C (−27 °C for chlorotrifluoroethylene). Furthermore, the symmetric ethene 1 leads to fewer byproducts than when using chlorotrifluoroethylene. The overall yields, however, do not differ much.

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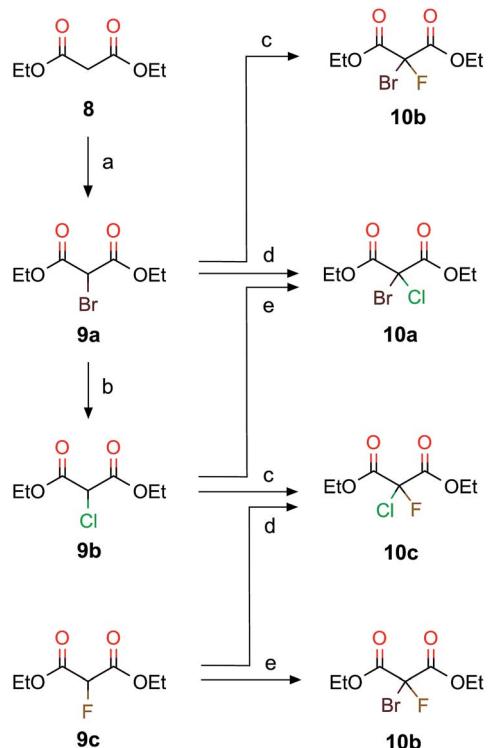
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[†] Electronic supplementary information (ESI) available: Experimental section including synthesis, characterization, NMR analysis and additional physico-chemical data. See DOI: 10.1039/c7ra09727a





Scheme 1 The pathway to obtain CHBrClF (7), modified from Doyle and Vogl^{22,39} and Beil *et al.*²¹



Scheme 2 The halogenated diethyl malonates **10a–c** were obtained by selective stepwise halogenation. (a) (1) NaH , rt , 2.5 h, (2) CuBr_2 , DMSO , 40°C , 1.5 h; (b) N -chlorosuccinimide, DMSO , rt , 24 h; (c) (1) NaH , rt , 3 h, (2) N -fluoro-2,4,6-trimethylpyridinium triflate, THF , 0°C , 10 min; (d) NaOCl , AcOH : acetone (2 : 5), 0°C , 1–3 h and (e) NaOBr , AcOH : acetone (2 : 5), 0°C , 12 h.

In this work we present pathways to obtain chiral haloacetic acids starting from diethyl malonate **8**. In comparison to past procedures starting from perhalogenated ethene^{20–22} for the synthesis of chiral halogenated acetic acids as just described in Scheme 1, the procedure advocated here has several advantages: (1) the reactant **8** is a common chemical reagent, cheap and easily accessible; (2) due to its CH acidity at the α -carbon atom it is a perfect starting material for halogenation reactions and (3) only a small number of reaction steps are needed. This paves the way to synthesize different dihalogenated diethyl malonates and, through decarboxylation, the corresponding halogenated acetic acids. Scheme 2 shows the halogenation reactions

explored to synthesize various combinations of brominated, chlorinated and fluorinated diethyl malonates together with the main reaction details. The yields from our reaction in Scheme 2 are summarized and compared to previous work in Table 1.

The halogenation of **8** with bromine leads to diethyl bromomalonate (**9a**) (experimental conditions are detailed in Scheme 2); the same reaction has been studied in the past by irradiating with light in the presence of Br_2 .³⁶ Following Scheme 2, diethyl chloromalonate (**9b**) was obtained from **9a** by replacing bromine with chlorine (99% yield), whereas diethyl fluoromalonate (**9c**) was inaccessible with usual mild fluorination agents. Fluorination is often performed with HF and triethylamine,^{41,42} which we did not try to reproduce in our laboratory since **9c** is commercially available. **9a** and **9b** have also been obtained from **8** in the presence of MgX_2 ($\text{X} = \text{Br}$, Cl , and I) under microwave irradiation.⁴³ We tested different methods to obtain **9b** directly from **8**, but these attempts resulted in poor yields and mainly the formation of diethyl dichloromalonate. However, the two step procedure from **8** to **9b** via **9a** is an efficient alternative.

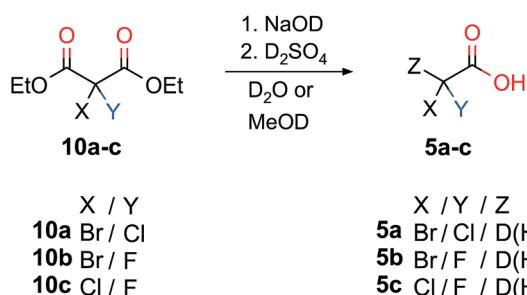
When the acidic hydrogen in **9a** is substituted with chlorine, we obtain the diethyl bromochloromalonate (**10a**, 97% yield). When optimizing the procedure described by Read and McMath,³⁵ Zimmer *et al.*³⁷ started from **8** and added bromine to synthesize **9a** and added SO_2Cl_2 to synthesize **10a**. Recently, **10a** was obtained from the diazo compound of diethyl malonate with a yield of about 90% (ref. 44) in the presence of a Cu-catalyst. Another way to synthesize **10a** is by the bromination of **9b** (100% yield). To obtain diethyl bromofluoromalonate (**10b**), we fluorinated **9a** (86% yield) or brominated **9c** (82% yield). Two routes are possible to synthesize diethyl chlorofluoromalonate (**10c**), either by fluorinating **9b** (73% yield) or chlorinating **9c** (86% yield). Thus, we successfully explored at least two different routes to synthesize diethyl dihalogenmalonates which enabled us to choose the pathway with the higher yield (see Table 1) and the most suitable reaction conditions.

Scheme 3 summarizes the synthetic pathways from a dihalogenated diethylmalonate to the corresponding dihalo acetic acid upon introducing D or H. Decarboxylation to the deuterated acetic acids **5a–c** was successfully performed for deuterio bromochloroacetic acid **5a** with a yield of 67%. Deutero bromofluoroacetic acid (**5b**, 51% yield) and deutero chlorofluoroacetic acid (**5c**, 49% yield) were also obtained.



Table 1 The yields (in %) for various intermediates and target compounds described in Schemes 2 and 3 compared to the literature (n.s.: not specified, mw.: microwave irradiation and l.i.: light induced)

Species	Yield (in %) and reference	Yield (in %) in this work
9a	83 (ref. 43) (mw.); 62 (ref. 45) (l.i.); 96 (ref. 46) (l.i.)	99
9b	81 (ref. 43) (mw.); 97 (ref. 47) (from ethyl 3,3-diethoxyacrylate)	99
10a	99 (ref. 48) (l.i.); 90 (ref. 44) (from diazo compound)	98 (from 9a); 100 (from 9b)
10b	—	86 (from 9a); 85 (from 9c)
10c	78 (ref. 49)	73 (from 9b); 86 (from 9c)
5a	n.s. ³⁷ (no deuteration, from 10a)	76 (deuterated ~ 89%, from 10a)
5b	32 (ref. 50 and 51) (deuterated ~ 95%, total 3 steps, from halogenated ethene)	51 (deuterated ~ 97%, from 10b)
5c	41 (ref. 51–53) (deuterated ~ 87%, total 3 steps, from halogenated ethene)	49 (deuterated ~ 94%, from 10c)
5d	19 (ref. 22); 36 (ref. 21) (total 4 steps, from halogenated ethene)	26 (from 10c)
7	50 to 70 (ref. 39) (from 5d)	46 (from 5d)

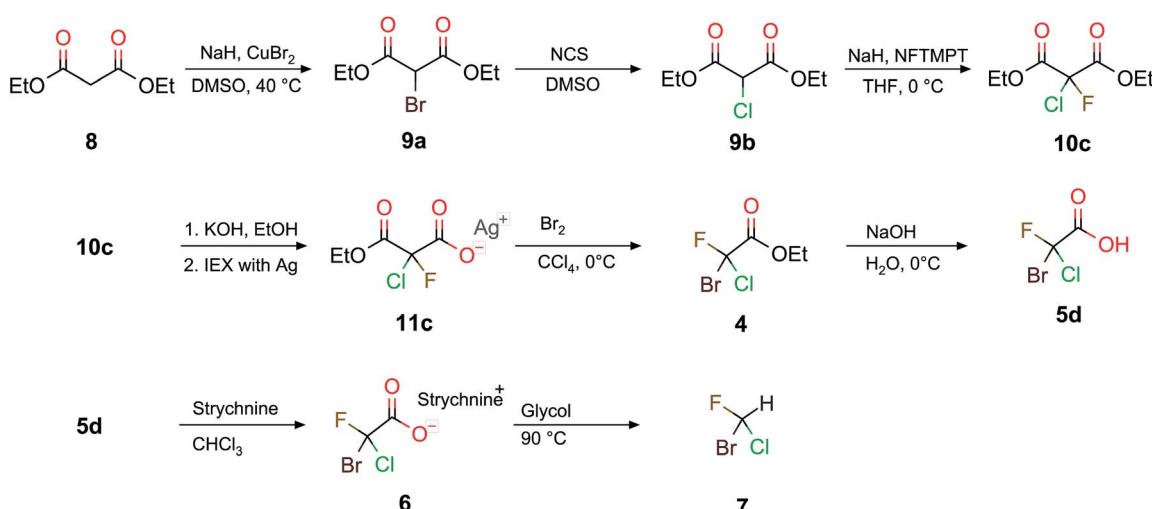


Scheme 3 The chiral acetic acids (**5a–d**) were obtained via the unilat- eral decarboxylation of the halogenated diethylmalonates (**10a–c**). For **5b** and **5c** the decarboxylation was carried out without NaOD to obtain **Z** = H.

Scheme 4 depicts the complete synthetic pathway from **8** to chiral halomethane **7**. The decarboxylation of **10c** to the bromochlorofluoroacetic acid **5d** (Scheme 4) requires two more reaction steps compared to the decarboxylation when D or H are inserted (see Scheme 2). Firstly, **10c** was saponified specifically to the monoethylester potassium salt. The Hunsdiecker decarboxylation⁵⁴ was carried out with the corresponding silver salt

(**11c**), which was obtained in a second step using a silver loaded ion exchange resin. Secondly, the resulting silver salt was then decarboxylated to obtain bromochlorofluoroacetate as product. The overall yield of these two steps was approximately 26% and the purity of the crude product was better than 80%. The decarboxylation was carried out with up to 20 mmol (\approx 6 g) of silver salt. Thirdly, a simple saponification of bromochlorofluoroacetate (**4**) with NaOH results in **5d** with a yield of 99%. Table 1 summarizes our results with respect to recent synthetic attempts to obtain monohalogenated (**9**), and dihalogenated (**10**) malonates, as well as the corresponding chiral halogenated acetic acids.

Based on the chiral halogenated acetic acids, the corresponding halomethanes were, in principle, accessible. The required decarboxylation procedure was described in the literature for the example of the bromochlorofluoroacetic acid **5d** to the corresponding halomethane CHBrClF (**7**).³⁹ We have repeated this reaction here with a yield of 48% and a purity of 99% compared to a 50 to 70% yield reported by Doyle and Vogl.³⁹ Although the overall yield of this 9 step synthesis is only approximately 12% (which is strongly affected by the 26% yield of the Hunsdiecker decarboxylation



Scheme 4 The synthesis pathway of this work to obtain **7** from **8** over a 9 step route. The steps from **8** to **10c** are a branch of Scheme 2.



from **11c** to **5d**), it turned out that the **11c** to **5d** step formed the reactant **10c** in a byreaction, therefore, **10c** could be reused again.

Experimental procedures

General conditions

A flow or an atmosphere of dry nitrogen was used with a Schlenk-apparatus for all water- and/or air-sensitive reactions. For the same purpose, the glassware was dried with a heat gun. Quantitative and qualitative characterization was performed using GC-MS and NMR (500 MHz). For the gas chromatography with mass spectrometry an InertCap 5MS/NP capillary column was used and the signals were recorded as the total ion current of the ions between *m/z* 50 and 500. The temperature method started as isothermal at 40 °C for 1 minute and was increased to 150 °C by 15 °C per minute. At a rate of 40 °C per minute, the oven was heated to 300 °C and was kept at this temperature for 1 minute. This resulted in a method length of 11 minutes and 45 seconds. ¹H, ¹³C and ¹⁹F NMR were recorded in parts per million and the data were reported as chemical shifts (δ) in parts per million (ppm), multiplicity, coupling constants (J) in Hz and integrals. The ¹³C NMR spectra were ¹H decoupled.

Commercial reagents were used with the given purity of the supplier. The purification of the intermediates was done using column chromatography if necessary. The given yields are the ¹H NMR purity corrected values. For comparison we list the ¹H NMR and GC-MS purities.

Diethyl bromomalonate 9a

The reaction apparatus was heated under vacuum and flushed with nitrogen before usage. Sodium hydride (12.9 g, 60%, 321.8 mmol) was suspended in dimethylsulfoxide (500 ml, anhydrous). Diethylmalonate **8** (50.2 g, 99%, 310.3 mmol) was slowly dropped into the suspension. The resulting mixture was added dropwise to a vigorously stirred solution of CuBr₂ (150.3 g, 99%, 666.0 mmol) in dimethylsulfoxide (275 ml, anhydrous). After the addition of ice water (200 ml) and H₂SO₄ (200 ml, 5%), the mixture was extracted with dichloromethane (3 × 200 ml). The combined organic layer was washed with water (3 × 200 ml), dried over Na₂SO₄ and then completely evaporated. The total yield of the colorless liquid was 81.0 g (99%) with a purity of 91.7% according to ¹H NMR (90.9% GC-MS).

¹H NMR (500 MHz, CDCl₃): δ 4.84 (s, 1H), 4.31 (q, J = 7.1 Hz, 4H), 1.33 (t, J = 7.1 Hz, 6H). ¹³C NMR (126 MHz, CDCl₃): δ 164.58 (s, 2C), 63.23 (t, 2C), 42.41 (d, 1C), 13.88 (q, 2C). GC-MS *t*_R 8.60 min.

Diethyl chloromalonate 9b

The reaction apparatus was heated under vacuum and flushed with nitrogen before usage. Diethyl bromomalonate **9a** (6.9 g, 98%, 28.2 mmol) was dissolved in dimethylsulfoxide (25 ml, anhydrous). *N*-Chlorosuccinimide (6.7 g, 99%, 49.0 mmol) was added and the mixture was stirred at room temperature overnight. After the addition of saturated ammonium chloride solution (20 ml) and water (50 ml), the mixture was extracted

with ethyl acetate (3 × 20 ml). The combined organic layers were washed with saturated NaCl solution (3 × 20 ml). The solvent was completely evaporated after drying with Na₂SO₄. The crude product was purified by column chromatography (cyclohexane : ethyl acetate, 5 : 1). The yield was 6.2 g (99.4%) with a purity of 88.0% according to ¹H NMR (83.4% GC-MS).

¹H NMR (500 MHz, CDCl₃): δ 4.86 (s, 1H), 4.32 (dq, J = 7.1 Hz, 1.1 Hz, 4H), 1.34 (t, J = 7.1 Hz, 6H). ¹³C NMR (126 MHz, CDCl₃): δ 164.50 (s, 2C), 63.18 (t, 2C), 55.47 (d, 1C), 13.91 (q, 2C). GC-MS *t*_R 7.89 min.

Diethyl bromochloromalonate 10a via chlorination

Diethyl bromomalonate **9a** (5.1 g, 89%, 19.0 mmol) was dissolved in acetone (40.0 ml) and acetic acid (16.0 ml). Sodium hypochlorite solution (19.0 ml, 10%, 25.5 mmol) was added dropwise during 30 min at 0 °C. Saturated NaHCO₃ solution (100 ml) was added to the reaction mixture. When the CO₂ evolution stopped (after approximately 15 min) the organic product layer was separated and the aqueous layer was extracted with dichloromethane (3 × 30 ml). The combined organic layers were washed with water (3 × 30 ml), dried over Na₂SO₄ and were completely evaporated. The yield was 5.5 g (98.0%) with a purity of 92.6% according to ¹H NMR (91.8% GC-MS).

¹H NMR (500 MHz, CDCl₃): δ 4.39 (q, J = 7.1 Hz, 4H), 1.36 (t, J = 7.1 Hz, 6H). ¹³C NMR (126 MHz, CDCl₃): δ 163.05 (s, 2C), 65.00 (s, 1C), 64.68 (t, 2C), 13.74 (q, 2C). GC-MS *t*_R 9.40 min.

Diethyl bromochloromalonate 10a via bromination

For the preparation of the sodium hypobromite solution, sodium hydroxide (3.0 g, 85%, 63.8 mmol) was dissolved in water (50 ml) and cooled to 0 °C. Bromine (3.3 g, 99%, 20.3 mmol) was added to the ice cold mixture and stirred for 30 min. In a separate flask diethyl chloromalonate **9b** (3.4 g, 99%, 17.3 mmol) was dissolved in acetone (10 ml) and acetic acid (5 ml) and cooled to 0 °C. The prepared sodium hypobromite solution was added dropwise to **9b**. The reaction mixture was stirred at RT overnight. The reaction mixture was added to saturated NaHCO₃ solution (20 ml) and extracted with dichloromethane (3 × 25 ml). The combined organic layers were washed with water (2 × 20 ml) and with saturated NaHCO₃ solution (2 × 20 ml), dried over Na₂SO₄ and were then completely evaporated. The total yield of the light brown liquid was 4.8 g (99.9%) with a purity of 98.5% according to ¹H NMR (99.1% GC-MS).

¹H NMR (500 MHz, CDCl₃): δ 4.38 (q, J = 7.1 Hz, 4H), 1.35 (t, J = 7.1 Hz, 6H). ¹³C NMR (126 MHz, CDCl₃): δ 163.02 (s, 2C), 64.99 (s, 1C), 64.67 (t, 2C), 13.73 (q, 2C). GC-MS *t*_R 9.40 min.

Diethyl bromofluoromalonate 10b via fluorination

Sodium hydride (80.0 mg, 60%, 2.0 mmol) was dissolved in tetrahydrofuran (5.0 ml, anhydrous). To the mixture diethyl bromomalonate **9a** (0.50 g, 99%, 2.0 mmol) was carefully added. After 3 h hydrogen evolution stopped and a clear solution was obtained. This solution was cooled to 0 °C. Then *N*-fluoro-2,4,6-trimethylpyridinium triflate (0.605 g, 99%, 2.1 mmol) was added. The reaction mixture was stirred at 0 °C for 30 min. To the reaction mixture water (10 ml) and hydrochloric acid (10 ml,



1 M) were added and it was then extracted with dichloromethane (3×20 ml). The combined organic layers were washed with saturated NaHCO_3 solution (2×10 ml) and water, sequentially. They were subsequently dried with Na_2SO_4 and evaporated completely. The yield of the light brown liquid was 0.57 g (85.5%) with a purity of 81.0% according to ^1H NMR (93.4% GC-MS).

^1H NMR (500 MHz, CDCl_3): δ 4.40 (q, $J = 7.1$ Hz, 4H), 1.37 (t, $J = 7.1$ Hz, 6H). ^{13}C NMR (126 MHz, CDCl_3): δ 162.33 (d, $J_{\text{CF}} = 26.46$ Hz, 2C), 89.95 (d, $J_{\text{CF}} = 270.9$ Hz, 1C), 64.29 (t, 2C), 13.78 (q, 2C). ^{19}F NMR (470 MHz, CDCl_3): δ -122.38 (s, 1F). GC-MS t_{R} 7.45 min.

Diethyl bromofluoromalonate 10b via bromination

The reaction procedure was similar to that of the bromination of **9b** to **10a**. Diethyl fluoromalonate **9c** (1.0 g, 97%, 5.4 mmol) was the reactant. 2 equivalents of NaOBr were used. The total yield of the light brown liquid was 1.25 g (84.9%) with a purity of 94.3% according to ^1H NMR (97.8% GC-MS).

^1H NMR (500 MHz, CDCl_3): δ 4.38 (q, $J = 7.1$ Hz, 4H), 1.34 (t, $J = 7.1$ Hz, 6H). ^{13}C NMR (126 MHz, CDCl_3): δ 162.28 (d, $J_{\text{CF}} = 26.46$ Hz, 2C), 89.93 (d, $J_{\text{CF}} = 270.9$ Hz, 1C), 64.27 (t, 2C), 13.74 (q, 2C). ^{19}F NMR (470 MHz, CDCl_3): δ -122.39 (s, 1F). GC-MS t_{R} 7.45 min.

Diethyl chlorofluoromalonate 10c via fluorination

The reaction procedure was similar to that of the fluorination of **9a** to **10b**. Diethyl chloromalonate **9b** (0.52 g, 97%, 2.6 mmol) was the reactant. The yield of the light brown liquid was 0.42 g (72.7%) with a purity of 97.5% according to ^1H NMR (97.4% GC-MS).

^1H NMR (500 MHz, CDCl_3): δ 4.38 (q, $J = 7.2$ Hz, 4H), 1.35 (t, $J = 7.2$ Hz, 6H). ^{13}C NMR (126 MHz, CDCl_3): δ 161.83 (s, 2C), 97.89 (d, $J_{\text{CF}} = 261.4$ Hz, 1C), 64.24 (t, 2C), 13.76 (q, 2C). ^{19}F NMR (470 MHz, CDCl_3): δ -161.83 (s, 1F). GC-MS t_{R} 6.68 min.

Diethyl chlorofluoromalonate 10c via chlorination

The reaction procedure was similar to that of the chlorination of **9a** to **10a**. Diethyl fluoromalonate **9c** (103.8 g, 97%, 565 mmol) was the reactant. The yield of the light brown liquid was 106.2 g (85.8%) with a purity of 97.1% according to ^1H NMR (93.9% GC-MS).

^1H NMR (500 MHz, CDCl_3): δ 4.38 (q, $J = 7.2$ Hz, 4H), 1.35 (t, $J = 7.2$ Hz, 6H). ^{13}C NMR (126 MHz, CDCl_3): δ 161.83 (s, 2C), 97.89 (d, $J_{\text{CF}} = 261.4$ Hz, 1C), 64.24 (t, 2C), 13.76 (q, 2C). ^{19}F NMR (470 MHz, CDCl_3): δ -161.83 (s, 1F). GC-MS t_{R} 6.68 min.

Deutero bromochloroacetic acid 5a

NaOD (0.75 g, 99%, 99% d-atom, 18.6 mmol) was dissolved in MeOD (10 ml) and added dropwise at room temperature to a solution of diethyl bromochloromalonate **10a** (1.5 g, 99%, 5.4 mmol) in MeOD (5 ml). The reaction mixture was stirred at room temperature for 30 min and a white suspension was formed. D_2SO_4 solution (5 g, 30%, 99% d-atom, 15.0 mmol) was added to the reaction mixture and the solid dissolved.

H_2SO_4 -solution (20 ml, 10%) was added and the reaction mixture was extracted with diethyl ether (3×20 ml). The combined organic layers were dried over Na_2SO_4 and evaporated to dryness. The yield of the light brown liquid was 0.75 g (75.7%) with a purity of 95.1% according to ^1H NMR (95.5% GC-MS). The degree of deuteration was ~89% and it was determined using the abundance ratio of m/z 172 and 173.

^1H NMR (500 MHz, CDCl_3): δ 8.80 (s, 1H). ^{13}C NMR (126 MHz, CDCl_3): δ 169.27 (s, 1C), 48.09 (t, $J_{\text{CD}} = 27.7$ Hz, 1C). GC-MS t_{R} 9.35 min.

Deutero bromofluoroacetic acid 5b

Diethyl bromofluoromalonate (1.25 g, 94%, 4.8 mmol) was added dropwise at room temperature to a solution of D_2SO_4 (5.0 g, 99%, 99% d-atom, 50.0 mmol) and D_2O (5.0 g). The reaction mixture was stirred at 120 °C for 5 hours. A solution of H_2SO_4 (20 ml, 5%) was added to the mixture and then it was extracted with diethyl ether (3×20 ml). The combined organic layers were dried over Na_2SO_4 and evaporated to dryness. The yield of the light brown liquid was 0.44 g (50.8%) with a purity of 84.0% according to ^1H NMR (90.3% GC-MS). The degree of deuteration was ~97% and it was determined using the abundance ratio of m/z 156 and 157.

^1H NMR (500 MHz, CDCl_3): δ 8.08 (s, 1H). ^{13}C NMR (126 MHz, CDCl_3): δ 166.50 (d, $J_{\text{CF}} = 25.5$ Hz, 1C), 81.25 (dt, $J_{\text{CF}} = 262.1$ Hz, $J_{\text{CD}} = 29.0$ Hz, 1C). ^{19}F NMR (470 MHz, CDCl_3): δ -151.96 (t, $J_{\text{CDF}} = 9.4$, 1F). GC-MS t_{R} 8.11 min.

Deutero chlorofluoroacetic acid 5c

Diethyl chlorofluoromalonate (1.5 g, 98%, 6.9 mmol) was added dropwise at room temperature to a solution of D_2SO_4 (7.0 g, 99%, 99% d-atom, 70.0 mmol) and D_2O (7.0 g). The reaction mixture was stirred at 120 °C overnight. A solution of H_2SO_4 (20 ml, 5%) was added to the mixture and then it was extracted with diethyl ether (3×20 ml). The combined organic layers were dried over Na_2SO_4 and evaporated to dryness. The yield of the light brown liquid was 0.41 g (48.5%) with a purity of 92.0% according to ^1H NMR (94.2% GC-MS). The degree of deuteration was ~94% and it was determined using the abundance ratio of m/z 61 and 62.

^1H NMR (500 MHz, CDCl_3): δ 10.81 (s, 1H). ^{13}C NMR (126 MHz, CDCl_3): δ 168.99 (d, $J_{\text{CF}} = 27.7$ Hz, 1C), 90.15 (dt, $J_{\text{CF}} = 253.3$ Hz, $J_{\text{CD}} = 29.0$ Hz, 1C). ^{19}F NMR (470 MHz, CDCl_3): δ -147.77 (t, $J_{\text{CDF}} = 4.7$, 1F). GC-MS t_{R} 7.11 min.

Potassium monoethyl chlorofluoromalonate

Diethyl chlorofluoromalonate **10c** (87.2 g, 93.9%, 385.3 mmol) was dissolved in absolute ethanol (250 ml). Potassium hydroxide (24.5 g, 86%, 374.9 mmol) was dissolved in absolute ethanol (250 ml) and added dropwise at room temperature to the vigorously stirred solution of **3c** within 4 h. The resulting suspension was filtered and the residue was washed with absolute ethanol (100 ml). The filtrate was completely evaporated. The solid product was washed with dichloromethane (150 ml) to remove the starting material. The pure product was obtained by



a second filtration and drying. The yield of the white crystalline solid was 52.3 g (61%) with a purity of approximately 100%.

¹H NMR (500 MHz, D₂O): δ 4.31 (q, *J* = 7.1 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (126 MHz, D₂O): δ 166.71 (d, *J_{CF}* = 24.1 Hz, 1C), 165.62 (d, *J_{CF}* = 28.4 Hz, 1C), 99.85 (d, *J_{CF}* = 260.0 Hz, 1C), 65.01 (t, 1C), 13.11 (q, 1C). ¹⁹F NMR (470 MHz, D₂O): δ -114.85 (s, 1F).

Silver monoethyl chlorofluoromalonate 11c

A highly acidic ion exchange resin (100 ml, Amberlite IR 120, Na⁺ form) was filled into a glass column. A solution of silver nitrate (400 ml, 0.4 M) was used to load the resin with silver ions. Before usage, the resin was washed until the eluting water was free of silver ions. An aqueous solution of potassium monoethyl chlorofluoromalonate (4.0 g, 0.018 mol, 0.03 g l⁻¹) was passed through the resin. The complete evaporation of the aqueous fraction gave 5.2 g (99%) of the silver monoethyl chlorofluoromalonate 11c as a grey solid with a purity of 100% (XRF and ¹⁹F NMR).

¹H NMR (500 MHz, D₂O): δ 4.44 (q, *J* = 7.1 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (126 MHz, D₂O): δ 165.70 (d, *J_{CF}* = 28.5 Hz, 1C), 161.81 (d, *J_{CF}* = 31.3 Hz, 1C), 97.29 (d, *J_{CF}* = 262.3 Hz, 1C), 65.00 (t, 1C), 13.72 (q, 1C). ¹⁹F NMR (470 MHz, D₂O): δ -121.17 (s, 1F).

Ethyl bromochlorofluoroacetate 4

Bromine (3.8 g, 99%, 23.7 mmol) was dissolved in CCl₄ (40 ml). At 0 °C, silver monoethyl chlorofluoromalonate 11c (6.0 g, 98%, 20.2 mmol) was added portion-wise (about 1.5 g per hour) while the reaction mixture was prevented from humidifying. After 1.5 h a continuous evolution of CO₂ started. When all of the reactant was added the mixture it was allowed to warm to room temperature and was then held at that temperature overnight. The precipitate was filtered and washed with CCl₄ (20 ml). Bromine was removed with NaHSO₃ solution (8%, 3 × 10 ml) and washed with saturated NaHCO₃ (3 × 10 ml). After drying with Na₂SO₄ the solvent was completely evaporated. The yield of the light brown liquid was 1.39 g (26.1%) with a purity of 82.6% according to ¹H NMR (82.0% GC-MS).

¹H NMR (500 MHz, CDCl₃): δ 4.45 (q, *J* = 7.1 Hz, 2H), 1.43 (t, *J* = 7.1 Hz, 4H). ¹³C NMR (126 MHz, CDCl₃): δ 161.90 (d, *J_{CF}* = 27.7 Hz, 1C), 96.12 (s, 1C), 64.83 (t, 1C), 13.75 (q, 1C). ¹⁹F NMR (470 MHz, CDCl₃): δ -64.23 (s, 1F). GC-MS *t_R* 4.38 min.

Bromochlorofluoroacetic acid 5d

NaOH (3.5 g, 85%, 74.4 mmol) was dissolved in water (30 ml). At 0 °C methyl bromochlorofluoroacetate 4 (12.9 g, 59%, 34.7 mmol) was added. After 3 h the acetate was quantitatively converted. The basic solution was acidified with concentrated H₂SO₄ (3 ml) and extracted with diethylether (3 × 20 ml). After drying with Na₂SO₄ the organic layer was completely evaporated. The yield of the colorless liquid was 9.0 g (99%) with a purity of 73.0% according to ¹H NMR (73.0% GC-MS).

¹H NMR (500 MHz, CDCl₃): δ 11.36 (s, 1H). ¹³C NMR (126 MHz, CDCl₃): δ 166.36 (d, *J_{CF}* = 28.0 Hz, 1C), 94.47 (d, *J_{CF}* = 315.0 Hz, 1C). ¹⁹F NMR (470 MHz, CDCl₃): δ -66.02 (s, 1F). GC-MS *t_R* 6.69 min.

Bromochlorofluoromethane 7

Bromochlorofluoroacetic acid 5d (9.0 g, 74%, 34.7 mmol) was dissolved in CHCl₃ (30 ml). Strychnin (11.6 g, 98%, 34.0 mmol) was dissolved in CHCl₃ (80 ml) and added to the acid at 0 °C over 30 minutes. After 1 h the CHCl₃ was evaporated and the strychnin salt was obtained quantitatively as a brownish solid. A portion of the strychnine bromochlorofluoroacetate (5.2 g, 99%, 8.76 mmol) was suspended in ethylene glycol (10 ml). The apparatus, which consisted of an Anschuetz head, Liebig condenser, collecting flask and cooling trap, was heated and flushed with nitrogen. The collecting flask and cooling trap were cooled with a mixture of acetone and dry ice to -78 °C. The suspension was heated to 80 °C and slowly increased to 100 °C as the gas formation also increased. After 45 min the gas formation stopped and the suspension was stirred at 140 °C for 1 h. The yield of the colorless liquid was 0.6 g (46.2%) with a purity of 95.2% according to ¹H NMR (99.0% GC-MS).

¹H NMR (500 MHz, CDCl₃): δ 7.64 (d, *J* = 52.0 Hz, 1H). ¹³C NMR (126 MHz, CDCl₃): δ 89.72 (dd, *J_{CF}* = 304.6 Hz, 1C). ¹⁹F NMR (470 MHz, CDCl₃): δ -81.66 (d, *J* = 52.0 Hz, 1F). GC-MS *t_R* 1.81 min.

Conclusion

In conclusion, we have presented an efficient and versatile pathway to obtain a large variety of chiral haloacetic acids from a common reagent which is easily commercially available. Further decarboxylation provides, in principle, access to the corresponding halomethanes. Currently, this has been explored only for the trihalogenated chiral acetic acids with success. Furthermore, the ability of obtaining the different haloacetic acids from a single reagent is another advantage. Our reagent 8 is also more easy to use compared to a differently halogenated ethene. The drawbacks of halogenated ethenes are clearly the low boiling points and their decreasing availability due to the CFC (chlorofluorocarbon) ban. CHBrClF 7 has been obtained starting from 8 by exploring the full reaction pathway (Scheme 4) described here. Chiral acetic acid has been obtained as a racemic mixture, however, it can be derivatized for enantioseparation (e.g. by preparative gas-chromatography⁵⁵ or by diastereomeric resolution¹⁹) along the reaction pathways shown in Schemes 3 and 4. This will then also remove minor impurities which may be present in the target compounds.

Conflicts of interest

There are no conflicts to declare.

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