

Fluorine gas for Life Science syntheses: Green metrics to assess selective direct fluorination for the synthesis of 2-fluoromalonate esters

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SUPPORTING INFORMATION

SI-1 Fluoromalonate green metrics calculations: Formulae

SI-2 Literature experimental procedures

SI-1 Fluoromalonate green metrics calculations: Formulae

The following formulae were used for calculating Atom Economy (AE), Reaction Mass Efficiency (RME) and Mass Intensity (MI) [1].

$$AE = \frac{\text{Molecular Weight of Product}}{\text{Total Molecular Weight of Reactants}} \times 100$$

$$RME = \frac{\text{Mass of Isolated Product}}{\text{Total Mass of Reactants}} \times 100$$

$$MI = \frac{\text{Total Mass in a Process or Process Step}}{\text{Mass of Product}}$$

The specific MI for Reaction, Solvents and Workup were calculated using the MI formula using only the corresponding data (total mass of reaction components, solvents and work-up components).

SI-2 Literature experimental procedures

Reported procedures for the synthesis of diethyl fluoromalonate do not always contain all the required information, therefore, some realistic assumptions were used where appropriate and are *highlighted* in the examples. Drying agents, when used, were not included in the calculations.

HFP process

The reported procedure [2] describes a four step procedure from hexafluoropropene (HFP) with two isolations. The literature procedure was reported for the methyl derivative, but yields for diethyl fluoromalonate and its intermediate precursor were also reported. For the calculations, the same scale was used using ethanol to synthesise the ethyl derivative. Procedures are directly taken from the appropriate literature reference.

Step 1.: 'Hexafluoropropene gas (255 g, 1.70 mol) was introduced into a solution of sodium methoxide (94 g, 1.74 mol) in methanol (500 mL), cooled in an ice-bath. The gas was completely absorbed in a course of 3 h. After 1 h of stirring at room temperature, the reaction mixture was poured into water (*1.5 L estimated*), and the resulting oily layer separated to give a crude product of 1,1,2,3,3,3-hexafluoropropyl methyl ether (400 mL). The oil was placed in a polyethylene vessel and concentrated sulfuric acid (400 mL) was added dropwise, keeping the temperature below 30 °C. The mixture was stirred for 1 h at room temperature, thrown into ice-water (*2 kg estimated*), the resulting oily layer was separated. After being washed with aq. NaHCO₃ solution (*100 g estimated*) then with water (*100 mL estimated*), it was dried over MgSO₄. Distillation gave methyl 2,3,3,3-tetrafluoropropionate (203 g, 74 %), bp 94 - 96 °C.'

Step 2.: 'To a solution of sodium methoxide (205 g, 3.8 mol) in methanol (800 mL) the methyl ester was added dropwise keeping the temperature below 30 °C. After 30 min of stirring at room temperature, the mixture was made acidic with cont. HCl (250 mL). The resulting suspension was stirred for 1 h at room temperature, filtered, and the filtrate was poured into ice water (*2.5 L estimated*). The oily material was extracted with ether (*500 mL estimated*) and the ethereal extract was washed with aq. NaHCO₃ solution (*200 mL estimated*), then with saturated NaCl solution (*200 mL estimated*), and dried over MgSO₄. Distillation under reduced pressure gave dimethyl fluoromalonate (137 g, 71%), bp. 111 - 112 °C/45 mmHg.'

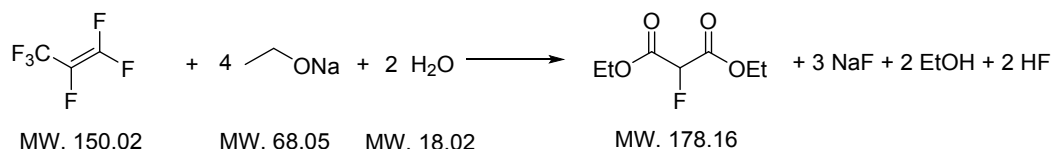
Reference to diethyl fluoromalonate: 'In a similar manner using sodium ethoxide in ethanol, ethyl 2,3,3,3-tetrafluoropropionate, bp. 108 - 109 °C was obtained in 82% yield. Diethyl fluoromalonate, bp. 110 - 111 °C/20 mmHg was then obtained in 63% yield.'

Amounts of chemicals used for calculation of HFP process:

Step 1.: Hexafluoropropene (255.0 g, 1.70 mol), NaOEt (118.4 g, 1.74 mol), ethanol (500 mL, 395 g), sulphuric acid (98%, 400 mL, 736 g), water (*estimated 3.5 kg*), NaHCO₃ solution (100 g estimated). Product: ethyl 2,3,3,3-tetrafluoropropionate (242.7 g, 82 % yield estimated).

Step 2.: Ethyl 2,3,3,3-tetrafluoropropionate (242.7 g, 1.39 mol), NaOEt (284.6 g, 4.18 mol), aqueous HCl (37%, 250 mL, 292.5 g), ethanol (800 mL, 631 g), water (*estimated 2.5 kg*), diethyl ether (*500 mL estimated*), NaHCO₃ solution (*200 g estimated*), saturated NaCl solution (*200 mL, 240 g estimated*). Diethyl fluoromalonate (156.4 g, 63 % yield for Step 2.).

Atom Economy:



$$AE(\text{HFP method}) = \frac{178.16}{150.02 + 4 \times 68.05 + 2 \times 18.02} \times 100 = 39.1$$

For Reaction Mass Efficiency calculations, the amount of water actually taking part in the reactions was fixed at 50 g per step, otherwise the large excess would produce unrealistic RME values.

$$RME(\text{HFP method}) = \frac{156.4}{255 + 403 + 100} \times 100 = 20.6$$

$$MI(\text{HFP method}) = \frac{255 + 403 + 6100 + 1026 + 736 + 300 + 292 + 357 + 240}{156.4} = 62.1$$

$$MI(\text{HFP Reaction}) = \frac{255 + 403 + 100 + 1026 + 736 + 292}{156.4} = 18.0$$

$$MI(\text{HFP Solvents}) = \frac{6000 + 1026 + 357 + 240}{156.4} = 48.8$$

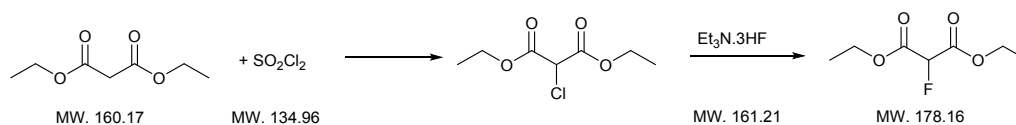
$$MI(\text{HFP Workup}) = \frac{6000 + 300 + 240 + 356}{156.4} = 44.1$$

Halogen exchange method

Diethyl chloromalonate: Sulfuryl chloride (154 g, 1.14 mmol) was added dropwise to diethyl malonate (181 g, 1.13 mol) at 60-70 °C and the mixture was stirred for 60 minutes. After this the mixture was heated to 160 °C for 20 minutes and distilled under vacuum (98-103 °C, 12 mbar) to afford diethyl chloromalonate (195 g, 88% yield).[3]

Diethyl fluoromalonate: Triethylamine tris(hydrofluoride) (137 g, 0.85 mol) and trimethylamine (86 g, 0.85 mol) were heated to 80 °C, diethyl chloromalonate (195 g, 1 mol) was added dropwise over 2 hours. The mixture was heated at 105-110 °C for 15 hours then cooled to 60 °C. Water (215 g) and xylenes (200 g) were added and the phases separated. The aqueous phase was extracted with xylenes (100 g) and the organic phase was distilled under vacuum to give diethyl fluoromalonate (156 g, 96% pure, 84 % yield).[4]

To assess this method, the scale of the two reactions were adjusted to give a linear sequence, assuming unaltered yields, stoichiometries, dilutions and conversions.



Amounts of chemicals used for Halex calculations:

Step 1.: Diethyl malonate (181 g, 1.13 mol), sulfuryl chloride (154 g, 1.14 mol), diethyl chloromalonate (195 g, 88 % yield).

Step 2.: Diethyl chloromalonate (195 g, 1.0 mol), triethylamine tris hydrofluoride (137 g, 0.85 mol), triethylamine (86 g, 0.85 mol), xylenes (300 g), water (215 g), diethyl fluoromalonate (156 g, 87 % yield).

$$AE(\text{Halex}) = \frac{178.16}{160.17 + 134.96 + 161.21} \times 100 = 39.2$$

$$RME(\text{Halex}) = \frac{156}{181 + 154 + 137} \times 100 = 33.0$$

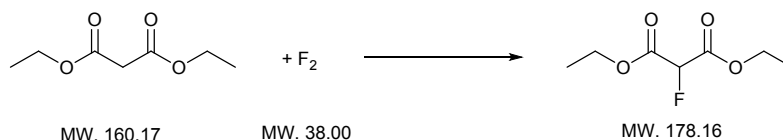
$$MI(\text{Halex}) = \frac{181 + 154 + 137 + 86 + 300 + 215}{156} = 6.9$$

$$MI(\text{Halex Reaction}) = \frac{181 + 154 + 137 + 86 + 300}{156} = 5.5$$

$$MI(\text{Halex Solvents}) = \frac{300 + 215}{156} = 3.3$$

$$MI(\text{Halex Workup}) = \frac{215 + 300}{156} = 3.3$$

Direct fluorination



Experimental procedures are contained in the main manuscript.

Amounts of chemicals used for direct fluorination

Diethyl malonate (40.0 g, 0.25 mol), copper nitrate hydrate (Cu(NO₃)₂·2.5H₂O; 5.81 g, 25 mmol), acetonitrile (200 mL, 157 g), fluorine gas (10.1, 266 mmol), water (50 mL, 50 g), ethyl acetate (100 mL, 90 g), saturated NaHCO₃ (25 g), brine (20 mL, 24 g), diethyl 2-fluoromalonate (44.4 g, 99% yield, 95 % purity) after distillation (34.7 g, 77 % yield, 99%+ purity).

$$AE(\text{Direct Fluorination}) = \frac{178.16}{160.17 + 38.00} \times 100 = 89.9$$

$$RME(\text{Direct Fluorination}) = \frac{44.4}{40.0 + 10.1} \times 100 = 88.6$$

$$RME(\text{Direct Fluorination Distilled}) = \frac{34.7}{40.0 + 10.1} \times 100 = 69.3$$

$$MI(\text{Direct Fluorination}) = \frac{40.0 + 5.8 + 157 + 10.1 + 50 + 90 + 25 + 24}{44.4} = 9.0$$

$$MI(\text{Direct Fluorination Distilled}) = \frac{40.0 + 5.8 + 157 + 10.1 + 50 + 90 + 25 + 24}{34.7} = 11.6$$

$$MI(\text{Direct Fluorination Reaction}) = \frac{40.0 + 5.8 + 10.1 + 157}{44.4} = 4.6$$

$$MI(\text{Direct Fluorination Reaction Distilled}) = \frac{40.0 + 5.8 + 10.1 + 157}{34.7} = 5.7$$

$$MI(\text{Direct Fluorination Solvents}) = \frac{157 + 50 + 90}{44.4} = 6.7$$

$$MI(\text{Direct Fluorination Solvents Distilled}) = \frac{157 + 50 + 90}{34.7} = 8.6$$

$$MI(\text{Direct Fluorination Workup}) = \frac{50 + 90 + 24 + 25}{44.4} = 4.3$$

$$MI(\text{Direct Fluorination Workup Distilled}) = \frac{50 + 90 + 24 + 25}{34.7} = 5.5$$

References

- [1] Constable, D. J. C.; Curzons, A. D.; Cunningham, V. L. *Green Chem.*, 2002, **4**, 521-527.
- [2] Ishikawa, N.; Takaoka, A.; Ibrahim, M. K., *J. Fluorine Chem.* 1984, **25**, 203-212.
- [3] Budesinsky, Z.; Budesinsky, M.; Svab, A. *Coll. Czechoslovak Chem. Commun.* 1981, **46**, 2254-2262.
- [4] Günther, A.; Weintritt, H.; Böhm, S. *WO2005019154*, 2005.