Fluorine gas for life science syntheses: green metrics to assess selective direct fluorination for the synthesis of 2-fluoromalonate esters†

Antal Harsanyi and Graham Sandford*

Optimisation and real time reaction monitoring of the synthesis of 2-fluoromalonate esters by direct fluorination using fluorine gas is reported. An assessment of green metrics including atom economy and process mass intensity factors, demonstrates that the one-step selective direct fluorination process compares very favourably with established multistep processes for the synthesis of fluoromalonates.

Recently, the concept of green chemistry has found widespread recognition in the chemical industries and various green chemistry related programs have been initiated both within and between major industrial companies. For example, several pharmaceutical companies now provide publicly available information on their solvent and reagent selection guides that were largely developed by their respective green chemistry groups. To assess the green credentials of a reaction, various mass balance based metrics have been developed and F factor, reaction mass efficiency (RME) and process mass intensity (PMI) are routinely assessed for process development campaigns. Such guides and metrics along with environmental, health and safety assessments form the basis of green metrics packages for the comparative assessment of alternative synthetic methods.

Large scale manufacture of most fluorinated systems are carried out using inexpensive anhydrous hydrogen fluoride (aHF) by, for example, very well established multi-step Balz-Schiemann6 and halogen exchange (Halex)7 processes respectively and subsequent functional group transformation of the resulting fluorinated aromatic building blocks. Whilst the use of aHF in industry is widespread, the highly corrosive, acidic nature of this reagent precludes fluorination reactions to appropriate, structurally simple organic substrates that are pre-functionalised by nitration or chlorination by, in many cases, multi-step procedures.

In principle, the most direct, least wasteful and economically viable method of fluorine introduction for large scale synthesis is the selective conversion of carbon–hydrogen bonds to carbon–fluorine bonds using inexpensive fluorine gas.8 However, despite advances in selective direct fluorination methodology, involving both batch and flow protocols, the use of fluorine gas for life science product manufacturing has so far been limited to the synthesis of 5-fluorouracil9 and a key intermediate for the synthesis of Voriconazole (V-Fend, Pfizer).10 However, although electrochemical cells used for the
production of fluorine gas\textsuperscript{11} are in operation in many silicon-wafer fabrication plants,\textsuperscript{12} precluding the use of fluorine gas in high pressure cylinders, selective direct fluorination technology has not been widely adopted by the life science industries.

The Durham group has reported the selective fluorination of various 1,3-diketones and ketoesters by both batch\textsuperscript{13} and continuous flow processes.\textsuperscript{14} Additionally, the synthesis of diethyl 2-fluoromalonate by direct fluorination has been previously achieved in good conversion, but the selectivity of the reaction was reported to be relatively low.\textsuperscript{15} Dialkyl 2-fluoromalonate esters could, in principle, be very useful fluorinated building blocks for the synthesis of fluorinated derivatives, and various alklylation,\textsuperscript{16} Michael addition\textsuperscript{17} and heterocycle formation\textsuperscript{18} processes have been described, providing an indication of the potential synthetic utility of this multi-functional, selectively fluorinated system.\textsuperscript{19} A growing number of patents utilising fluoromalonate as a substrate for the synthesis of a range of biologically active systems have been published recently\textsuperscript{20} and reviewed.\textsuperscript{19} For example, Fluoxastrobin (Fandango\textregistered), a fungicide marketed by Bayer CropScience that has achieved global annual sales of over €140 m since its launch in 2005,\textsuperscript{21} and TAK-733, an anti-cancer drug candidate,\textsuperscript{22} employ 2-fluoromalonate esters as the key fluorinated starting material (Scheme 1).

There are three realistic, low-cost synthetic strategies available for the large scale manufacture of diethyl 2-fluoromalonate ester (Scheme 2) which involve reaction of ethanol with hexafluoropropene (HFP),\textsuperscript{23} halogen exchange (Halex)\textsuperscript{24} and selective direct fluorination\textsuperscript{15} processes. Other syntheses of fluoromalonate esters using electrophilic fluorinating agents such as Selectfluor\textsuperscript{TM} are possible, but are not sufficiently commercially attractive to be considered for manufacture on the large scale.
In this paper, we reassess and optimise the direct fluorination of diethyl malonate, catalysed by copper nitrate, with a view to intensifying this transformation and reducing its overall environmental impact. Upon optimisation, a comparison of the green metrics of selective direct fluorination with corresponding literature HFP and Halex routes for the synthesis of fluoromalonates to determine the relative merits of the three possible routes.

Results and discussion

Before a comparison of the green metrics between the three possible, economically viable large scale processes for the synthesis of fluoromalonate esters (Scheme 2) could be carried out, some primary goals for the optimisation of the process were targeted: complete conversion of the starting material is essential because it can be difficult to separate the starting material from the desired monofluorinated product by simple distillation; fluorine gas usage should be minimised because neutralisation of excess reagent could potentially generate significant amounts of waste; reduction in volumes of solvents used to reduce waste streams and overall intensification of the fluorination process and replacement and/or reduction of all environmentally harmful solvents used.

Conventional batch direct fluorination reactions of malonate esters were carried out in glassware vessels by introduction of fluorine gas, as a 10% or 20% mixture in nitrogen (v/v), at a prescribed rate via a gas mass flow controller into a solution of malonate ester and copper nitrate catalyst in acetonitrile using equipment described previously. To better understand the relationship between fluorine gas introduction and rate of conversion, real time IR spectroscopic monitoring of the reaction was chosen as the most suitable technique. The use of the ReactIR technique was enabled by a sufficient difference in the carbonyl group stretching frequencies (1734 cm$^{-1}$ for diethyl malonate and 1775 cm$^{-1}$ for diethyl 2-fluoromalonate) and provided an in situ reaction profile (Fig. 1).

The real time reaction monitoring (Fig. 1 and 2) revealed that the reaction begins instantly upon initiation of fluorine introduction and the reaction conversion is directly proportional to the amount of fluorine gas passed into the reaction vessel. When the intensity of the fluoromalonate carbonyl peak (1775 cm$^{-1}$) reached a maximum, the introduction of fluorine gas was stopped and the crude reaction mixture was analysed by $^1$H and $^{19}$F NMR spectroscopy. Complete conver-

![Fig. 1](image1)

**Fig. 1** IR spectra of the fluorination reaction at 0% (light blue), 50% (dark blue) and 100% (red) conversions.

![Fig. 2](image2)

**Fig. 2** In situ monitoring of the fluorination of diethyl malonate.
Fluorination of diethyl malonate ester using fluorine gas catalysed by Cu(NO₃)₂·2.5H₂O

The concentration of fluorine gas, between 10–20% v/v in nitrogen, does not affect the selectivity of the reaction and the quality of the product either, as exemplified by the product mixtures obtained from reactions 1, 2 and 7 which have identical compositions. In contrast, carrying out fluorination reactions at room temperature rather than cooling the reaction mixture to 0–5 °C leads to increased catalyst decomposition which results in an insoluble copper species that on occasion blocked the fluorine gas inlet tube. In addition, without cooling, the exothermic nature of this fluorination reaction led to a slight reaction temperature increase (from 20 to 29 °C in a small scale laboratory experiment) resulting in loss of some solvent and some decomposition of the catalyst and product degradation.

Lowering the concentration of the copper nitrate catalyst led to a significantly slower reaction as would be expected and required the use of a larger excess of fluorine gas to enable sufficiently high conversion. For example, the reaction proceeded in the presence of only 2.5 mol% catalyst, but in this case 40% excess fluorine was required to reach 100% conversion.

Typical literature work-up procedures for direct fluorination reactions involve pouring the reaction mixture into 3 to 5 volumes of water and extracting the resulting mixture three times with dichloromethane. The combined organic fraction is typically washed with water, saturated sodium bicarbonate solution and dried over sodium sulfate before evaporation of the solvent to give the crude reaction product. We sought to improve the work-up to enable recycling of the reaction solvent and substitute the use of environmentally harmful dichloromethane in the reaction work-up stage. Upon completion of fluorine gas addition, acetonitrile was evaporated for reuse and then the residue was partitioned between ethyl acetate and water, the organic phase was washed with water, saturated Na₂CO₃ solution and saturated brine and dried prior to evaporation under reduced pressure. Modification of the workup procedure in this manner enables the recovery of acetonitrile and...
ethyl acetate and significantly reduces the amount of aqueous waste generated. When direct reuse of the recovered acetonitrile was attempted, a copper containing precipitate was formed presumably because of the high HF content of the solvent (0.63 M by titration). Therefore, before reuse of the solvent, HF must be removed. Stirring the recovered reaction solvent with solid Na₂CO₃ lowered the acid content to an acceptable level (0.04 M) and when a second fluorination reaction was carried out in the recovered, neutralised acetonitrile, no change in the fluorination reaction profile was observed.

Upon completion of these optimisation studies, selective fluorination reactions of malonate esters were scaled up to 40 g scale in the laboratory without experiencing any change in product profile. Isolation of significant quantities of mono-fluoromalonate A crude product (99% yield, 95% purity) was achieved which could be used in the subsequent cyclisation processes described below without further purification or, if high purity material was required, could be purified by fractional vacuum distillation (bp. 102–103 °C, 18 mbar) to produce 99% pure material in 77% yield.

Related malonate esters were also subjected to direct fluorination using the optimised conditions established above. In the case of di-tert-butyl malonate, fluorination was carried out on 12 g scale. 100% conversion was reached after the introduction of 1.2 equivalents of fluorine gas and the desired product was isolated in 96% yield. The purity of the crude product was higher than 97% by ¹H and ¹⁹F NMR spectroscopy without any further purification and as expected, the only side product was the 2,2-difluorinated product (Scheme 3).

From an atom economy point of view, methyl ester derivatives are preferable substrates compared to ethyl or other higher alkyl esters since they lead to smaller quantities of waste and so the fluorination of dimethyl malonate was investigated. Using 10% catalyst and 1.1 equivalent of fluorine, 20 g of dimethyl malonate was fluorinated to afford dimethyl fluoromalonate in 97% yield and 95% purity after isolation by simple work-up and no further purification. In this case, the only side product was dimethyl 2,2-difluoromalonate which was separated from dimethyl fluoromalonate by fractional distillation to afford high purity dimethyl fluoromalonate which crystallises at room temperature (Fig. 3).

Condensation of fluoromalonate esters with dinucleophiles is a convenient route to multifunctional fluorinated heterocyclic scaffolds. A number of nitrogen dinucleophiles were
Select direct fluorination (SDF) process for the synthesis of 2-fluromalonate esters have been optimised on a reasonable scale in the laboratory (40 g scale) both in terms of product yield and purity (99% crude yield, 95% purity, after distillation 77% yield and 99% purity) and green reaction metrics. The PMI value of the SDF process is, even at this relatively small scale, under 10, a benchmark figure that demonstrates an effective, environmentally benign chemical synthesis.

As described in the patent literature, Bayer’s halogen exchange reaction is a very efficient process, the reaction uses only a minimum amount of solvent and all process metrics look very promising apart from low atom economy due to the use of Et,N-3HF. A possible disadvantage of the halogen exchange process is the reported possibility of several time consuming vacuum distillation procedures, but this may not be necessary on the manufacturing scale.

Table 2  Synthesis of fluorinated heterocycles using crude (95% pure) diethyl fluoromalonate ester

<table>
<thead>
<tr>
<th>Dinucleophile</th>
<th>Product</th>
<th>Yield/%</th>
</tr>
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<tbody>
<tr>
<td>H₂N₂H₂</td>
<td><img src="image1.png" alt="Dinucleophile Product 1" /></td>
<td>51</td>
</tr>
<tr>
<td>H₂N₂H₂</td>
<td><img src="image2.png" alt="Dinucleophile Product 2" /></td>
<td>86</td>
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<tr>
<td>H₂N₂H₂</td>
<td><img src="image3.png" alt="Dinucleophile Product 3" /></td>
<td>64</td>
</tr>
<tr>
<td>H₂N₂H₂</td>
<td><img src="image4.png" alt="Dinucleophile Product 4" /></td>
<td>68</td>
</tr>
</tbody>
</table>

with sulfonyl chloride is reasonably selective and pure diethyl chloromalonate can be obtained in good yield after vacuum distillation and it is reasonable to assume that this reaction is suitable for large scale synthesis. The halogen exchange reaction is also very efficient since HF:amine systems are convenient, reactive sources of fluoride ion and additionally, they can be handled safely since they are less volatile than aHF and are commercially available on the multi-tonne scale (Table 3).

The first obvious advantage of the direct fluorination process is that diethyl fluoromalonate is obtained in one synthetic step in excellent yield and no purification is necessary to achieve sufficiently pure material for subsequent synthetic steps (99% yield, 95% purity). The yields of the HFP and Halex methods are significantly lower and vacuum distillation processes are reported to be used to obtain the desired purity. The atom economy and reaction mass efficiency of the direct fluorination reaction are significantly higher than those of the competing synthetic processes mostly because fluorination only requires a single synthetic step and the only significant side product is one equivalent of HF. The low atom economy of the halogen exchange is explained by the high molecular weight reagents used for both the chlorination (SO₂Cl₂) and the halogen exchange (Et₃N-3HF) steps. The PMI metrics indicate how much waste is generated during the production of 1 kg of product, and solvents are key contributors. However, for the direct fluorination process, solvents used in the reaction (MeCN) and work-up procedure (EtOAc) may be recovered and reused with no change in product profile.

In particular, crude diethyl fluoromalonate prepared above reacts efficiently with formamidine to give 5-fluoro-4,6-dihydroxy pyrimidine, a key intermediate in the synthesis of Fluoxastrobins, in good yield (64%), which is comparable with previously reported 61–78% yields (Table 2).

To compare the metrics of the optimised direct fluorination process with other methods for the synthesis of fluoromalonate esters, a “first pass” metrics package, was implemented. Hexafluoropropene (HFP) is an important, inexpensive per-fluorinated building block used for the synthesis of various well known fluoropolymers and refrigerant gases and is, therefore, available on the industrial scale. Synthesis of fluoromalonates by reaction of HFP with ethanol and H₂SO₄ affords good purity product in fair yield, but, from an environmental impact point of view, this is a very wasteful and low-atom economy process. Firstly, the synthesis of the starting material requires many steps, ultimately by reaction of low molecular weight hydrocarbons with chlorine gas and subsequent halogen exchange in a very energy intensive process and, secondly, a significant amount of hazardous, strongly acidic waste is generated in the reaction of HFP with ethanol.

The halogen exchange reaction requires the industrial synthesis of high purity chloromalonate ester since the purity of the final fluoromaloneate product largely depends on the efficiency and selectivity of this step. The chlorination reaction
Experimental

General

Proton, fluorine and carbon nuclear magnetic resonance spectra (1H, 19F and 13C NMR) were obtained using a Bruker 400 Ultrashield spectrometer (1H NMR at 400 MHz, 19F NMR at 376 MHz and 13C NMR at 101 MHz) using residual solvent peaks as the internal standard (1H NMR: CHCl3 at 7.26 ppm, 19F NMR: CFCl3 at 0.00 ppm and 13C NMR: CDCl3 at 77.16 ppm). NMR spectroscopic data are reported as follows: chemical shift (ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz) and assignment.

GC-MS data were obtained using a Trace GC-MS device (Thermo-Finnigan Corporation) operating in electron impact ionization (EI) mode. Accurate mass analysis was performed on a Xevo QToF mass spectrometer (Waters Ltd, UK) with an accurate solids analysis probe (ASAP). Melting point data were obtained using a Gallenkamp apparatus at atmospheric pressure and are uncorrected. Infra-red (IR) spectroscopy was performed on a Perkin Elmer 1600 Series FTIR with an ATR probe. In situ IR spectroscopy was performed using a Mettler Toledo React IR instrument equipped with a diamond probe.

Fluorinations were carried out in a glass fluorination reactor (100 mL, 250 mL or 500 mL) unless otherwise stated. The reactor was built from a standard glass bottle with GL 45 thread joint and a PTFE screw cap or a glass flange head, equipped with a gas inlet/outlet head built of Stainless Steel, PTFE and FEP Swagelok components as described in earlier publications.15

Vacuum distillations were carried out using FISCHER® micro SPALTROHR®-column MMS 255 with manual fraction collection.

Diethyl malonate fluorination: general reaction

Diethyl malonate (3.20 g, 20 mmol) and copper nitrate hydrate (Cu(NO3)2·2.5H2O; 0.46 g, 2 mmol) were dissolved in acetonitrile (17 mL) and placed into the fluorination reactor and the mixture was cooled to 0–5 °C. After purging the system with N2 for 5 minutes, fluorine gas (10% v/v in N2, 45 mL min−1, 22 mmol) was passed into the stirred mixture for 2 h. The reactor was purged with nitrogen for 10 minutes, the solvent was removed in vacuo and the residue partitioned between water (10 mL) and ethyl acetate (10 mL). The aqueous phase was extracted with ethyl acetate (10 mL) and the combined organic layers were washed with saturated brine (10 mL). After drying over sodium sulfate, the solvent was evaporated to leave diethyl 2-fluoromalonate (3.37 g, 94% yield, 93.5% purity) as a colourless liquid. IR (neat, cm−1): 2986, 1747, 1243, 1187, 1097, 1020; δH (CDCl3, 400 MHz) 1.31 (6H, t, 3JHH 7.2, CH3), 4.31 (4H, q, 3JHH 7.2, CH2), 5.26 (1H, d, 2JHF 48.3, CHF); δF...
Diethyl fluoromalonate large scale fluorination

Diethyl malonate (40.0 g, 0.25 mol) and copper nitrate hydrate (Cu(NO₃)₂·2H₂O; 5.81 g, 25 mmol) were dissolved in acetonitrile (200 mL) and placed in 500 mL fluorination vessel, cooled to 0–5 °C and stirred at 650 rpm using an overhead stirrer. After purging the system with N₂ for 5 minutes, fluorine gas (20% v/v in N₂, 80 mL min⁻¹) was introduced into the reaction mixture for 7 h. After purging with nitrogen for 20 minutes, the solvent was evaporated to leave diethyl 2-fluoromalonate (34.7 g, 77% yield, 99% purity) as a colourless liquid, bp. 112 °C, m.p.: >300 °C; IR (neat, cm⁻¹) 2980, 1744, 1369, 1213; δF (ASAP) 131 (100%, [M + H]+).21

Dimethyl 2-fluoromalonate

Dimethyl malonate (19.8 g, 0.15 mol) and Cu(NO₃)₂·2H₂O (3.50 g, 15 mmol) were dissolved in acetonitrile (85 mL), the mixture was cooled to 0–5 °C and stirred at 650 rpm using an overhead stirrer. After purging the system with N₂ for 5 minutes, fluorine gas (20% v/v in N₂, 50 mL min⁻¹) was introduced into the mixture for 6 hours and 30 minutes. The reactor was purged with nitrogen for 10 minutes, the solvent was evaporated to give dimethyl 2-fluoromalonate (44.4 g, 99% yield, 95% purity) as a light yellow, transparent liquid, bp. 102–103 °C (18 mbar), (lit.: 110–112 °C, 29 mbar), spectroscopic data as above.

5-Fluoro-4,6-dihydroxypyrimidine

Formamidine acetate (2.06 g, 20 mmol) was added to the solution of sodium (1.38 g, 60 mmol) in anhydrous ethanol (40 mL) and the mixture was heated to reflux. Diethyl 2-fluoromalonate (3.20 g, 18 mmol) was added dropwise over 20 minutes and the mixture was heated at reflux for 6 h. After cooling to room temperature, the solution was evaporated to dryness, the residue was dissolved in water (20 mL), acidified with HCl (5 mL), the precipitate was filtered, washed with water (5 mL), ethanol (2 × 5 mL) and diethyl ether (2 × 5 mL). After drying in vacuo, 5-fluoro-4,6-dihydroxypyrimidine (1.50 g, 64%) was obtained as a brown powder. m.p.: >300 °C; [M + H]+, 131.0244, C₄H₄FN₂O₂ requires: [M]+, 131.0257; IR (neat, cm⁻¹) 3053, 2639, 1633, 1547, 1388, 1213; δF (DMSO, 400 MHz) 7.90 (1H, s, C=O); δF (CDCl₃, 376 MHz): 193.79 (d, 4JCF 196.5, C=O), 164.39 (d, 4JCF 15.0, C–F), 132.79 (d, 4JCF 235.6, C–F), 144.46 (d, 4JCF 7.7, C–H).22

2-Amino-5-fluoro-4,6-dihydroxypyrimidine

Guanidine sulfate (5.95 g, 55 mmol) was added to the solution of sodium (2.50 g, 110 mmol) in anhydrous ethanol (100 mL) and the mixture was heated to reflux. Diethyl 2-fluoromalonate (8.90 g, 50 mmol, 93% pure) was added dropwise over 20 minutes and the mixture was heated at reflux for 6 h. After cooling to room temperature, the solution was evaporated to dryness, the residue was dissolved in water (20 mL), neutralised with HCl to pH 7, the precipitated product was filtered, washed with water (5 mL), ethanol (2 × 5 mL) and diethyl ether (2 × 5 mL). After drying in vacuo, 2-amino-5-fluoro-4,6-dihydroxy- pyrimidine (6.21 g, 86%) was obtained as a pink powder. m.p.: >300 °C [M + H]+, 146.0357, C₄H₄FN₂O₂ requires: [M]+, 146.0366); IR (neat, cm⁻¹) 3343, 3100, 2916, 2731, 1600, 1557,
1415, 1358, 1204; δ_H (DMSO d_6, 400 MHz) 7.00 (2H, bs, N−H), 11.1 (2H, bs, OH); δ_C (DMSO d_6, 376 MHz): 197.05 (s); δ_C (DMSO d_6, 100 MHz) 125.13 (d, J_CF 208.6, C−F), 149.26 (d, J_CF 2.3, C−H), 155.12 (d, J_CF 18.0, C−OH); m/z (APSA) 146 (100%), [M + H]$.^{18}$

5-Fluorobarbituric acid

Urea (1.50 g, 25 mmol) was added to the solution of sodium (1.2 g, 53 mmol) in anhydrous ethanol (50 mL) and the mixture was heated to reflux. Diethyl 2-fluoromalonate (4.45 g, 25 mmol) was added dropwise over 10 minutes and the mixture was heated at reflux for 1 h. After cooling to room temperature, the solution was filtered, the residue was washed with ethanol (20 mL), dissolved in water (30 mL) and acidified with HCl to pH 1. The precipitated product was recrystallized from the liquor to afford 5-fluorobarbituric acid (1.87 g, 51%) as a tan powder. m.p.: >300 °C; [M + H]+, 147.0206; IR (neat, cm$^{-1}$) 2926, 2828, 1578, 1383, 1128; δ_C (D_2O + NaOD, 376 MHz): 191.95 (s); δ_C (D_2O + NaOD, 100 MHz) 131.89 (d, J_CF 214.4, C−F), 137.77 (d, J_CF 6.2, C−NH), 164.59 (d, J_CF 13.4, C=O); m/z (APSA) 147 (25%, [M + H]+).$^{18}$

3-Fluoro-1-H,1,5-benzodiazepine-2,4-dione

O-Phenylenediamine (2.70 g, 25 mmol) was added to the solution of sodium (1.2 g, 53 mmol) in anhydrous ethanol (50 mL) and the mixture was heated to reflux. Diethyl 2-fluoromalonate (4.45 g, 25 mmol) was added dropwise over 10 minutes and the mixture was heated at reflux for 1 h. After cooling to room temperature, the solution was filtered, the residue was washed with ethanol (20 mL), dissolved in water (30 mL) and acidified with HCl to pH 1. The mixture was cooled in ice, filtered, washed with water (2 × 10 mL) and dried in vacuo to afford 3-fluoro-1-H,1,5-benzodiazepine-2,4-dione (3.23 g, 68%) as a tan powder. m.p.: >300 °C; [M + H]+, 195.0567; C_H_F_N_O requires: [M]+, 195.0550; IR (neat, cm$^{-1}$) 2934, 2971, 2727, 1681, 1500, 1159; δ_H (DMSO d_6, 400 MHz): 5.57 (1H, d, J_HH 46.4, CHF), 7.15−7.19 (2H, m, Ar−H), 7.22 (2H, dt, J_HH 6.6, J_HF 3.5, Ar−H), 10.81 (2H, bs N−H); δ_C (DMSO d_6, 376 MHz): 207.99 (d, J_CHF 46.4 C−F); δ_C (DMSO d_6, 100 MHz) 85.12 (d, J_CF 184.5, C−F), 122.55, 125.52, 128.41, 163.36 (d, J_CF 23.2, C−O), 164.59 (d, J_CF 13.4, C=O); m/z (APSA) 195 (100%, [M + H]+), 135 (23%, [M − COCHF]+).$^{23b}$

Acknowledgements

The research included in this publication received funding from the European Community’s Seventh Framework Programme (FP7/2007–2013) and EFPIA companies’ in kind contribution for the Innovative Medicine Initiative under Grant Agreement no. 115360 (Chemical manufacturing methods for the 21st century pharmaceutical industries, CHEM21). We thank Dr D. S. Yufit for X-ray crystallographic analyses and Dr C. R. McElroy for useful discussions regarding the use of green metrics.

References


