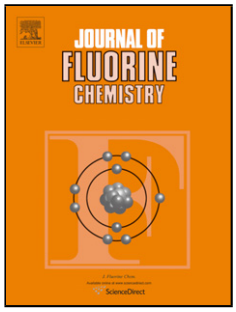

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Synthesis of β-fluoro(dicarbonyl)ethylamines from 2-fluoro-ethylacetoacetate and dimethyl-2-fluoromalonate ester by batch and semi-continuous flow three-component Mannich reactions

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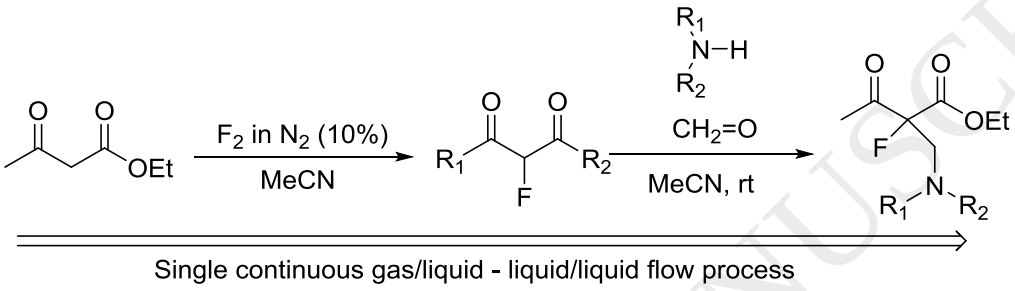
Graphical abstracts



Highlights

- Mannich reactions of fluoroketoester and fluoromalonates successful
- Polyfunctional β-fluoro(dicarbonyl)ethylamines synthesised
- Semi continuous flow gas/liquid liquid/liquid flow process

Abstract

Multi-component Mannich reactions between 2-fluoro-ethylacetoacetate or dimethyl-2-fluoromalonate ester, aldehyde and amine components allowing convenient synthesis of β-fluoro(dicarbonyl)ethylamine systems using both batch and continuous flow techniques are reported.

1. Introduction

The incorporation of fluorine atoms into pharmaceutical candidates is a well-established approach to, for example, affect lipophilicity, pK_a and metabolic stability of new chemical entities as part of drug discovery programs [1]. While many pharmaceuticals bearing fluorine atoms attached to aromatic rings are currently commercially available, lead compounds with fluorine atom attached to sp_3 carbon are increasingly appearing in pharmaceutical company pipelines [2] and, consequently, effective and inexpensive methodology for the synthesis of selectively fluorinated multifunctional building blocks for incorporation into drug synthesis campaigns are very desirable. However, the building block approach relies on the ready availability of a wide range of inexpensive fluorinated substrates of differing functionality and the establishment of appropriate reactivity profiles [3].

Recently, we reported the optimized synthesis of 2-fluoromalonate esters by a direct fluorination strategy [4] which is very efficient, inexpensive, does not generate significant waste and is readily scalable. Analogous selective direct fluorination routes using fluorine gas to corresponding 2-fluoro-ketoesters [5] have also been developed and scaled up by industry [6]. Surprisingly, however, reactions of 2-fluoro malonate ester and 2-fluoro-ketoester derivatives are not particularly well developed despite the anticipated synthetic potential of these polyfuctional substrates and we recently reviewed the chemistry of fluoromalonate substrates to indicate some of the synthetic utility of these systems [7]. For example, in the context of developing the use of dimethyl 2-fluoro-malonate ester for the synthesis of more structurally complex fluorinated intermediates, we established routes to various fluoroheterocyclic systems [8].

In this paper, we describe the use of 2-fluoro-ethylacetoacetate **1** and dimethyl 2-fluoromalonate ester **2** in multi-component (MCR) Mannich reactions. The first reported MCR was the Strecker synthesis of the α-amino nitrile in 1850 [9] [4] and since then, MCR chemistry has been extensively developed. Well-known examples of MCRs are associated mainly with reactions of carbonyl compounds, used as substrates in the Biginelli reaction, the Hantzsch dihydropyridine synthesis and, particularly, Mannich-type reactions [10] giving rapid access to large libraries of molecules possessing a high degree of functionality and structural diversity.

However, while carbonyl compounds have played a crucial role in the development of multi-component reactions, use of corresponding fluorinated carbonyl compounds have been much less investigated as MCR substrates. Applications of Mannich-type reactions utilizing fluorinated carbonyl substrates have been reported previously [11] such as, for example, the synthesis of β-fluoronitro(phenylsulfonyl)ethylamines from fluoro-ketosulfone substrates described by Prakash and Olah [12]. Of particular relevance to the research reported here, Zhang and coworkers developed a Mannich reaction involving various fluoro-ketoesters catalyzed by zinc nitrate and irradiated by microwave at high temperature [13].

Here we use 2-fluoroethylacetoacetate **1** and dimethyl 2-fluoromalonate ester **2** as MCR components in Mannich reactions involving formaldehyde or benzaldehyde and different types of amines as educts to give polyfunctional fluorinated products bearing amine and carbonyl functionalities by both batch and continuous flow protocols in simple, scalable reaction processes.

2. Results and discussion

In initial studies we investigated reactions of 2-fluoro-ethylacetoacetate **1** with an amine **3** and formaldehyde in multi component Mannich-type processes (Table 1). Reactions were carried out by first mixing both amine **3** and formalin together before addition of the fluorinated dicarbonyl substrate **1** in order to limit the formation of any alcohol by-product by Aldol condensation. Our optimized conditions were found to be 1.7 equivalents of amine **3** and 1.5 equivalents of formaldehyde, stirred together for two hours at room temperature, preceding the addition of the 2-fluoro-ethylacetoacetate **1** and further reaction at room temperature. Reactions involving less reactive amines such as benzylamine were carried out at 90°C, providing the corresponding Mannich products **4** in full conversion. Analogous reactions between 2-ethyl 2-fluoro-acetoacetate **1** with an amine **3** and benzaldehyde were also performed in high yields (Table 2).

During the course of this work, related Mannich reactions of fluorinated 1,3-dicarbonyl compounds catalyzed by $Zn(NO_3)_2$ using microwave irradiation at 120 ^oC were reported [13]. However, the method we have described above does not require such vigorous heating and allows access to various products from, for example **5b** and **5c**, which reportedly cannot be obtained by the zinc nitrate catalyzed method [13]. Furthermore, Mannich reactions of fluoromalonate ester **2** were not described using the zinc catalyzed method.

Many organic reactions have been adapted to laboratory scale continuous flow processes and the advantages of flow techniques such as mass transfer, reaction control and continuous operation are now well established [14]. Mannich reactions have been performed in continuous flow micro-fluidic devices [15] and asymmetric anti-Mannich reactions in continuous flow packed bed reactor [16] using various polystyrene-supported chiral amine-based catalyst have also been reported. We have previously reported continuous flow fluorination reactions using fluorine gas in gas-liquid processes including fluorination of ketoester and diester substrates [17].

Following optimization of continuous flow reactions of ethyl fluoro-ethylacetoacetate **1** with amine/formaldehyde mixtures in a one-step liquid-liquid flow process, we adapted our synthetic procedure described above to a two-step gas-liquid, liquid-liquid semi-continuous flow process using stainless steel coiled tube reactors (Fig. 1) that we have described previously [18]. A schematic diagram of the process is shown in Figure 1. Fluorine gas in nitrogen (10% *v/v*) was introduced into input 1 of the first coiled steel tube reactor and passed along the tube concurrently with ethyl acetoacetate in acetonitrile which was simultaneously added to the reactor system via inlet 2. The flow of the gaseous reactant stream was controlled by gas mass flowmeter and the liquid dicarbonyl reagent solution was introduced by hplc pump so that the fluorine gas : dicarbonyl addition ratio was *ca.*1.3 : 1. The flow rate of each reagent was adjusted to ensure a retention time of 2 to 5 min of the dicarbonyl substrate within the tubular reactor. The crude product mixture for the fluorination reaction was collected in a gas liquid separator flask where liquid was collected and gaseous waste passed through a scrubbing tower filled with soda-lime. The crude

fluoro-dicarbonyl product mixture was then pumped without any work-up procedure directly into input 3 of the second continuous flow coiled steel tube reactor while, simultaneously, a solution containing the amine and aldehyde solution was added at a controlled flow rate via Input 4. The crude product mixture for the two-step one continuous flow process was collected and, following work-up, the Mannich products were isolated in good yield and purity confirming the efficiency of this semi continuous flow process strategy (Table 4).

Combined gas-liquid liquid-liquid sequential flow reaction using fluorine gas have not been well developed and only examples demonstrating the synthesis of fluoropyrazole derivatives have been recorded [19]. The reasonable yields of Mannich products **4** obtained from fluorine, ketoester and aminal inputs in the two-step one semi-continuous flow process demonstrates the possible opportunities for process intensification of multi-step synthetic strategies using fluorine gas.

In summary, a direct Mannich-type three component MCR reaction has been developed for the ready synthesis of β-fluoro(dicarbonyl)ethylamine derivatives starting from fluorinated dicarbonyl substrates further demonstrating that such systems are particularly useful as starting substrates for further transformations or functionalization, opening up opportunities for the synthesis of more complex fluorinated systems for life science projects from simple, readily accessible fluorinated systems.

3. Experimental

3.1 General

All the chemicals and solvents used were commercially purchased from Alfa Aesar, Apollo Scientific, Fluorochem or Sigma Aldrich and, unless otherwise stated, were

used without any further purification. 1,3-Dimethyl-2-fluoromalonate was synthesized as described previously [4c].

Proton, fluorine and carbon nuclear magnetic resonance spectra (^{1}H, ^{19}F, ^{13}C NMR) were obtained using a Bruker 400 Ultrashield spectrometer (^{1}H NMR at 400 MHz, ^{19}F NMR at 376 MHz and ^{13}C NMR at 101 MHz) using residual solvent peaks as the internal standard (^{1}H NMR; $CDCl_3$ at 7.26 ppm, ^{19}F NMR; $CFCl_3$ at 0.00 ppm and ^{13}C NMR; $CDCl_3$ at 77.16 ppm). NMR spectroscopic data are reported as follows: chemical shift (ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quarter, 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) or a TQD UPLC (Waters) instrument operating in electrospray ionization mode.

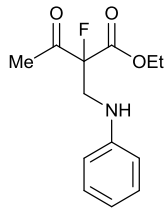
Mannich-type reaction by conventional batch process.

General procedure: In a 50 mL two-necked flask containing dichloromethane (10 mL) were added the amine (17 mmol) followed by the aldehyde (15 mmol) and the resulting reaction mixture was allowed to stir at rt for 2 h., before the fluorinated dicarbonyl system (10 mmol) was added. The reaction mixture was stirred at rt for 16 h, evaporated and the residue dissolved in dichloromethane (20 mL), washed with distilled water (2 x 20 mL), dried over magnesium sulfate and evaporated, to give the desired product. Further purification by distillation or column chromatography eluting from hexane/ethyl acetate was carried out when appropriate.

Analytical and spectroscopic data for each individual compound are listed below. For NMR data only resonances of one diastereoisomer or conformer is given for clarity.

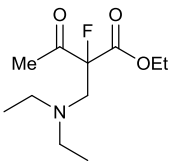
Mannich reactions of 2-Fluoro ethylacetoacetate and formaldehyde

Ethyl-2-((benzylamino)methyl)-2-fluoro-3-oxobutanoate 4a



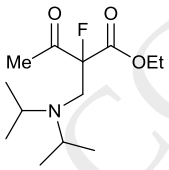
^{1}H NMR (400 MHz, *CDCl$_3$*) δ_H 1.31 (t, *J* = 7.1 Hz, 3H, -OCH$_2$C*H$_3$*), 2.39 (d, *J* = 4.8 Hz, 3H, -C(O)C*H$_3$*), 3.80 – 4.08 (m, 2H, -CF-C*H$_2$*), 4.28 (q, *J* = 7.1 Hz, 2H, -OC*H$_2$*CH$_3$), 6.63 – 6.95 (m, 3H, ArH), 7.12 – 7.24 (m, 2H, ArH). ^{19}F NMR (376 MHz, *CDCl$_3$*) δ_F -169.37 (tq, $^{3}J_{HF}$ = 22.4 Hz, $^{4}J_{HF}$ = 4.8 Hz). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ_C 13.97 (-OCH$_2$*C*H$_3$), 26.27 (-C(O)*C*H$_3$), 47.53 (d, $^{2}J_{CF}$ = 20.5 Hz, -CF-*C*H$_2$), 62.96 (-O*C*H$_2$CH$_3$), 100.23 (d, $^{1}J_{CF}$ = 198.8 Hz, -*C*F), 113.62 (Ar), 118.80 (Ar), 129.27 (Ar), 147.17 (Ar), 165.01 (d, $^{2}J_{CF}$ = 25.4 Hz, -*C*(O)O), 201.35 (d, $^{2}J_{CF}$ = 28.6 Hz, -*C*(O)CH$_3$). MS (ESI) m/z 115.02 (100%), 123.98 (68.4%), 224.12 (62.7%), 254.15 ([M+H]$^+$, 72.2%). HRMS (ESI) m/z calcd for [M+H]$^+$ C$_{13}$H$_{17}$FNO$_3$ 254.1200, found 254.1192.

Ethyl-2-((diethylamino)methyl)-2-fluoro-3-oxobutanoate 4b



^{1}H NMR (400 MHz, *CDCl$_3$*) δ_H 0.87 (t, *J* = 7.1 Hz, 6H, –NCH$_2$C*H$_3$*), 1.22 (t, *J* = 7.1 Hz, 3H, -OCH$_2$C*H$_3$*), 2.23 (d, $^{4}J_{HF}$ = 5.0 Hz, 3H, -C(O)C*H$_3$*), 2.51 (q, *J* = 7.1, 4H, –NC*H$_2$*CH$_3$), 3.05 (t, $^{3}J_{HF}$ = 26.1, 2H, -CF-C*H$_2$*), 4.18 (q, *J* = 7.1 Hz, 2H, -OC*H$_2$*CH$_3$). ^{19}F NMR (376 MHz, *CDCl$_3$*) δ_F -166.64 (tq, $^{3}J_{HF}$ = 26.1 Hz, $^{4}J_{HF}$ 5.0 Hz). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ_C 11.45 (NCH$_2$*C*H$_3$), 13.86 (-OCH$_2$*C*H$_3$), 26.41 (-C(O)*C*H$_3$), 47.89 (m, –N*C*H$_2$CH$_3$), 56.42 (d, $^{2}J_{CF}$ = 18.4 Hz, -CF-*C*H$_2$), 62.18 (-O*C*H$_2$CH$_3$), 102.21 (d, $^{1}J_{CF}$ = 199.1 Hz, -*C*F), 165.39 (d, $^{2}J_{CF}$ = 26.0 Hz, -*C*(O)O), 201.94 (d, $^{2}J_{CF}$ = 29.6 Hz, -*C*(O)CH$_3$). MS (ESI) m/z 234.07 ([M+H]$^+$, 100%), 86.04 ([M-C$_6$H$_8$FO$_3$]$^+$, 95.3%), 266.10 (81.7%). HRMS (ESI) m/z calcd for [M+H]$^+$ C$_{11}$H$_{21}$FNO$_3$ 234.1505; found 234.1504.

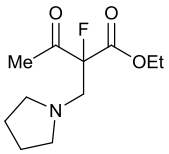
Ethyl-2-((diisopropylamino)methyl)-2-fluoro-3-oxobutanoate 4c



^{1}H NMR (400 MHz, *CDCl$_3$*) δ_H 0.97 (d, *J* = 6.7 Hz, 12H, -CH(C*H$_3$*)$_2$), 1.32 (t, *J* = 7.1 Hz, 3H, -OCH$_2$C*H$_3$*), 2.32 (d, $^{4}J_{HF}$ = 5.1 Hz, 3H, -C(O)C*H$_3$*), 3.08 (m, 2H, -CF-C*H$_2$*), 3.24 (m, 2H, -C*H*(CH$_3$)$_2$), 4.13 – 4.39 (m, 2H, -OC*H$_2$*CH$_3$).^{19}F NMR (376 MHz, *CDCl$_3$*) δ_F -163.81 (ddq, $^{3}J_{HF}$ = 22.3 Hz, $^{3}J_{HF}$ = 20.8 Hz, $^{4}J_{HF}$ - 4.7 Hz). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ_C 13.98 (-OCH$_2$*C*H$_3$), 20.66 (s, -CH(*C*H$_3$)$_2$), 26.87 (-C(O)*C*H$_3$), 48.66 (s, -N*C*H), 49.45 (d, $^{2}J_{CF}$ = 18.7 Hz, -CF-*C*H$_2$), 62.29 (-O*C*H$_2$CH$_3$), 102.78 (d, $^{2}J_{CF}$ = 198.7 Hz, -*C*F), 165.72 (d, $^{2}J_{CF}$ = 26.0 Hz, -*C*(O)O), 202.63 (d, $^{2}J_{CF}$ = 30.3 Hz, -*C*(O)CH$_3$). MS (ESI) m/z 102.10 ([M-C$_7$H$_{10}$FO$_3$•]$^+$, 100%), 114.10 ([M-C$_6$H$_8$FO$_3$•]$^+$, 77.9%), 262.13 ([M+H]$^+$, 74.3%),

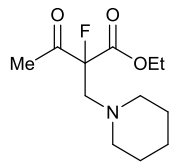
294.2 (55.8%). HRMS (ESI) m/z calcd for $[M+H]^+$ $C_{13}H_{25}FNO_3$ 262.1818; found 262.1803.

Ethyl-2-(pyrrolidin-1-methyl)-2-fluoro-3-oxobutanoate 4d



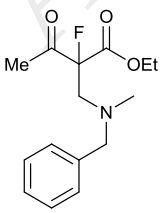
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.25 (t, *J* = 7.1 Hz, 3H, -OCH$_2$C*H$_3$*), 1.66 – 1.86 (m, 4H, -C*H$_2$*), 2.27 (s, 3H, -C(O)C*H$_3$*), 2.49-2.65 (m, 4H, -NC*H$_2$*), 3.06-3.31 (m, 2H, -CFC*H$_2$*), 4.10-4.36 (m, 2H, -OC*H$_2$*CH$_3$). ^{19}F NMR (376 MHz, *CDCl$_3$*) δ_F -166.84 (ddq, $^3J_{HF}$ = 29.7 Hz, $^3J_{HF}$ = 25.1 Hz, $^4J_{HF}$ = 4.8 Hz). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ_C 13.93 (-OCH$_2$*C*H$_3$), 23.83 (*C*H$_2$), 26.23 (-C(O)*C*H$_3$), 55.28 (-N*C*H$_2$), 58.41 (d, $^2J_{CF}$ = 19.4 Hz, -CF-*C*H$_2$), 62.34 (-O*C*H$_2$CH$_3$), 101.62 (d, $^1J_{CF}$ = 199.2 Hz, *C*F), 165.35 (d, $^2J_{CF}$ = 25.8 Hz, -*C*(O)O), 201.39 (d, $^2J_{CF}$ = 28.6 Hz, -*C*(O)CH$_3$). MS (ESI) m/z 232.10 ($[M+H]^+$, 100%), 264.18 (56.4%), 84.01 ($[M-C_5H_6FO_4^{\bullet}]^+$, 49.3%). HRMS (ESI) m/z calcd for $[M+H]^+$ $C_{11}H_{19}FNO_3$ 232.1349; found 231.1350.

Ethyl-2-(piperidin-1-methyl)-2-fluoro-3-oxobutanoate 4e



^{1}H NMR (400 MHz, *CDCl$_3$*) δ_H 1.29 (t, *J* = 7.1 Hz, 3H, -OCH$_2$C*H$_3$*), 1.35 – 1.46 (m, 2H, -C*H$_2$*), 1.48 – 1.60 (m, 4H, C*H$_2$*), 2.30 (d, $^4J_{HF}$ = 4.9 Hz, 3H, -C(O)C*H$_3$*), 2.49 – 2.57 (m, 4H, -NC*H$_2$*), 3.02 (d, $^3J_{HF}$ = 26.8 Hz, -CF-C*H$_2$*), 4.09 – 4.43 (m, 2H, -OC*H$_2$*CH$_3$). ^{19}F NMR (376 MHz, *CDCl$_3$*) δ_F -165.59 (tq, $^3J_{HF}$ = 26.6, $^4J_{HF}$ = 4.9 Hz). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ_C 14.01 (-OCH$_2$*C*H$_3$), 23.84 (*C*H$_2$), 26.18 (*C*H$_2$), 26.40 (-C(O)*C*H$_3$), 55.82 (s, N*C*H$_2$), 61.10 (d, $^2J_{CF}$ = 18.5 Hz, -CF-*C*H$_2$), 62.30 (-O*C*H$_2$CH$_3$), 102.16 (d, $^1J_{CF}$ = 199.9 Hz, -*C*F), 165.40 (d, $^2J_{CF}$ = 25.8 Hz, -*C*(O)O), 201.75 (d, $^2J_{CF}$ = 29.3 Hz, -*C*(O)CH$_3$). MS (ESI) m/z 246.31 ($[M+H]^+$, 100%). HRMS (ESI) m/z calcd for $[M+H]^+$ $C_{12}H_{21}FNO_3$ 246.1505; found 246.1508.

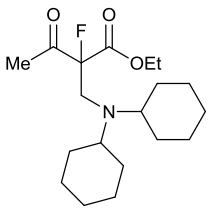
Ethyl-2-((benzylmethylamino)methyl)-2-fluoro-3-oxobutanoate 4f



^{1}H NMR (400 MHz, *CDCl$_3$*) δ_H 1.30 (t, *J* = 7.1 Hz, 3H, -OCH$_2$C*H$_3$*), 2.26 (m, 3H, -NC*H$_3$*), 2.34 (d, $^4J_{HF}$ = 4.7 Hz, 3H, -C(O)C*H$_3$*), 3.24 (t, $^3J_{HF}$ = 26.0, 2H, -CFC*H$_2$*), 3.63 (s, 2H, -NC*H$_2$*), 4.28 (q, *J* = 7.2 Hz, 2H, -OC*H$_2$*CH$_3$), 7.09 – 7.41 (m, 5H, ArH). ^{19}F NMR (376 MHz, *CDCl$_3$*) δ_F -166.35 (tq, $^3J_{HF}$ = 25.8, $^4J_{HF}$ = 4.8 Hz). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ_C 14.02 (-OCH$_2$*C*H$_3$), 26.27 (-C(O)*C*H$_3$), 43.40 (d, $^4J_{CF}$ = 3.2 Hz, -N*C*H$_3$), 59.84 (d, $^2J_{CF}$

= 18.4 Hz, -CF-*C*H$_2$), 62.50 (-O*C*H$_2$CH$_3$), 63.51 (d, $^4J_{CF}$ = 2.5 Hz, -NCH$_2$), 102.16 (d, $^1J_{CF}$ = 199.5 Hz, *C*F), 127.12 (Ar), 128.22 (Ar), 128.90 (Ar), 138.59 (Ar), 165.36 (d, $^2J_{CF}$ = 26.0 Hz, -*C*(O)O), 201.13 (d, $^2J_{CF}$ = 28.8 Hz, -*C*(O)CH$_3$). MS (ESI) m/z 122.23 ([C$_8$H$_{10}$N$^\bullet$]$^+$, 100%), 282.23 ([M+H]$^+$, 90.5%), 300.36 (72.4%). HRMS (ESI) m/z calcd for [M+H]$^+$ C$_{15}$H$_{20}$FNO$_3$ 282.1505 ; found 282.1516.

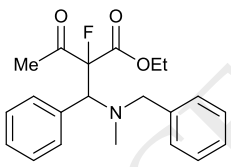
Ethyl-2-((dicyclohexylamino)methyl)-2-fluoro-3-oxobutanoate 4g



^{1}H NMR (400 MHz, *CDCl$_3$*) δ$_H$ 0.85 – 1.86 (m) (23H, CH$_2$ and CH$_3$), 2.19 (d, $^4J_{HF}$ = 5.2 Hz, 3H, -C(O)C*H$_3$*), 2.36 – 2.56 (m, 2H, NC*H*), 3.14 - 3.35 (m, 2H, -CF-C*H$_2$*), 3.90 – 4.26 (m, 2H, -OC*H$_2$*CH$_3$). ^{19}F NMR (376 MHz, *CDCl$_3$*) δ$_F$ -171.87 (ddq, $^3J_{HF}$ = 26.6 Hz, $^3J_{HF}$ = 21.8 Hz, $^4J_{HF}$ 4.8 Hz). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ$_C$ 13.83 (-OCH$_2$*C*H$_3$), 25.16, 25.92, 26.00 (*C*H$_2$), 26.75 (-C(O)*C*H$_3$), 50.28 (d, $^2J_{CF}$ = 18.5 Hz, -CF*C*H$_2$), 52.92 (N-*C*H), 62.07 (-O*C*H$_2$CH$_3$), 102.82 (d, $^1J_{CF}$ = 198.9 Hz, -*C*F), 165.55 (d, $^2J_{CF}$ = 26.0 Hz, -*C*(O)O), 202.48 (d, $^2J_{CF}$ = 30.3 Hz, -*C*(O)CH$_3$). MS (ESI) m/z 182.2 ([C$_{12}$H$_{22}$N$^\bullet$+H]$^+$, 100%), 191.3 ([M-C$_6$H$_8$FO$_3^\bullet$]$^+$, 28.9%), 312.4 (38.5%), 342.4 ([M+H]$^+$, 31.5%), HRMS (ESI) m/z calcd for [M+H]$^+$ C$_{19}$H$_{33}$FNO$_3$ 342.2444, found 342.2445.

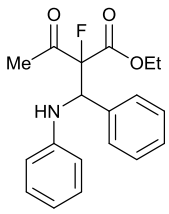
Mannich reactions of fluorinated dicarbonyl systems and benzaldehyde

Ethyl-2-(phenyl(benzylmethylamino)methyl)-2-fluoro-3-oxobutanoate 5a



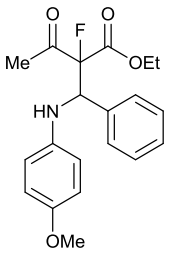
^{1}H NMR (400 MHz, *CDCl$_3$*) δ$_H$ 0.96 (t, *J* = 7.1 Hz, 3H, -OCH$_2$C*H$_3$*), 2.13 (d, $^4J_{HF}$ = 5.6 Hz, 3H, -C(O)C*H$_3$*), 2.16 (s, 3H, -NC*H$_3$*), 3.46 - 3.67 (m, 2H, -N-C*H$_2$*), 3.96 – 4.13 (m, 2H, -OC*H$_2$*CH$_3$), 4.88 (d, $^3J_{HF}$ = 35.0 Hz, 1H, -CF-C*H*), 7.08 – 7.97 (m, 10H, ArH).^{19}F NMR (376 MHz, *CDCl$_3$*) δ$_F$ -176.64 (dq, $^3J_{HF}$ = 34.6, $^4J_{HF}$ = 5.5 Hz). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ$_C$ 13.59 (OCH$_2$*C*H$_3$), 26.99 (-C(O)*C*H$_3$), 38.92 (-N*C*H$_3$), 61.00 (-N-*C*H$_2$), 62.39 (-O*C*H$_2$CH$_3$), 70.79 (d, $^2J_{CF}$ = 15.8 Hz, -CF-*C*H), 105.73 (d, $^1J_{CF}$ = 209.4 Hz, -*C*F), 126.98, 128.15, 128.25, 128.74, 129.00, 130.25, 134.44, 138.99 (Ar), 164.57 (d, $^2J_{CF}$ = 25.5 Hz, -*C*(O)O), 201.85 (d, $^2J_{CF}$ = 30.6 Hz, -*C*(O)CH$_3$). MS (ESI) m/z 122.2 ([C$_8$H$_{10}$N$^\bullet$], 100%), 282.3 ([M-C$_6$H$_5^\bullet$+H]$^+$, 26.6%), 358.2 ([M+H]$^+$, 6.0%) HRMS (ESI) m/z calcd for [M+H]$^+$ C$_{21}$H$_{24}$FNO$_3$ 358.1818; found 358.1825.

Ethyl-2-(phenyl(phenylamino)methyl)-2-fluoro-3-oxobutanoate 5b



^{1}H NMR (400MHz, *CDCl$_3$*) δ_H 1.12 (t, *J* = 7.1 Hz, 3H, -OCH$_2$C*H$_3$*), 1.96 (d, $^{4}J_{HF}$ = 5.8 Hz, 3H, -OC*H$_3$*), 4.13 (q, *J* = 7.1 Hz, 2H, -OC*H$_2$*CH$_3$), 5.47 (d, $^{4}J_{HF}$ = 27.9, 1H, -CF-C*H*), 6.63 – 6.87 (m, 2H, ArH), 7.23 – 7.48 (m, 3H, ArH), 7.23 – 7.48 (m, 5H, ArH), 8.50 (s, 1H, N*H*). ^{19}F NMR (376 MHz, *CDCl$_3$*) δ_F -179.28 (dq, $^{3}J_{HF}$ = 28.1, $^{4}J_{HF}$ = 5.9 Hz). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ_C 13.99 (-OCH$_2$*C*H$_3$), 26.65 (-C(O)*C*H$_3$), 60.51 (d, $^{2}J_{CF}$ = 18.3 Hz, -CF-*C*H), 63.10 (-O*C*H$_2$CH$_3$), 103.03 (d, $^{1}J_{CF}$ = 204.7 Hz, -*C*F), 114.47, 118.52, 119.29, 125.95, 128.48 – 128.66 (m), 131.39, 135.47, 145.46 (Ar), 164.61 (d, $^{2}J_{CF}$ = 24.3 Hz,-*C*(O)O), 201.05 (d, $^{2}J_{CF}$ = 28.3 Hz, -*C*(O)CH$_3$). MS (ESI) m/z 182.08 ([M- C$_6$H$_8$FO$_3^{\bullet}$]$^+$, 100%), 330.17 ([M+H]$^+$, 34.0%). HRMS (ESI) m/z calcd for [M+H]$^+$ C$_{19}$H$_{21}$FNO$_3$ 330.1505; found 330.1510.

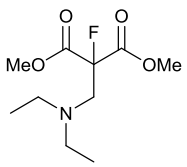
Ethyl-2-(phenyl(4-methoxyphenylamino)methyl)-2-fluoro-3-oxobutanoate 5c



^{1}H NMR (400 MHz, *CDCl$_3$*) δ_H 1.27 (t, *J* = 7.2 Hz, 3H, -OCH$_2$C*H$_3$*), 1.94 (d, $^{4}J_{HF}$ = 5.7 Hz, 3H, -C(O)C*H$_3$*), 3.70 (s, 3H, -OC*H$_3$*), 4.24-4.39 (m, 2H, -OC*H$_2$*CH$_3$), 5.34 (d, $^{3}J_{HF}$ = 28.2 Hz, 1H, -CF-C*H*), 6.60-6.73 (m, 2H, ArH), 6.68-6.73 (m, 2H, ArH), 7.13-7.46 (m, 5H, ArH). ^{19}F NMR (376 MHz, *CDCl$_3$*) δ_F -179.57 (dq, $^{3}J_{HF}$ = 28.2 Hz, $^{4}J_{HF}$ = 5.8 Hz). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ_C 14.01 (-OCH$_2$*C*H$_3$), 26.63 (-C(O)*C*H$_3$), 55.55 (-O*C*H$_3$), 61.74 (d, $^{2}J_{CF}$ = 18.2 Hz, -CF-*C*H), 63.01 (-O*C*H$_2$CH$_3$), 103.21 (d, $^{1}J_{CF}$ = 204.6 Hz, -*C*F), 114.67 (Ar), 128.43 – 128.59 (m, Ar), 135.56 (Ar), 139.37 (Ar), 153.04 (*C*-OMe), 164.57 (d, $^{2}J_{CF}$ = 26.7 Hz, -*C*(O)O), 200.99 (d, $^{2}J_{CF}$ = 29.5 Hz, -*C*(O)CH$_3$). MS (ASAP) m/z 212.11 ([M-C$_6$H$_8$FO$_3^{\bullet}$]$^+$, 100%), 360.17 ([M+H]$^+$, 1.9%). HRMS (ASAP) m/z calcd for [M]$^+$ C$_{20}$H$_{22}$FNO$_4$ 359.1533; found 359.1538.

Mannich reactions of 2-Fluoro-1,3-dimethymalonate and formaldehyde

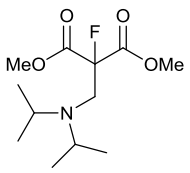
Dimethyl-2-((diethylamino)methyl)-2-fluoromalonate 6a



^{1}H NMR (400 MHz, *CDCl$_3$*) δ_H 0.91 (t, *J* = 7.1 Hz, 6H,–CH$_2$C*H$_3$*), 2.57 (q, *J* = 7.1 Hz, 4H, C*H$_2$*CH$_3$), 3.17 (t, $^{3}J_{HF}$ = 26.2 Hz, 2H, -CF-C*H$_2$*), 3.78 (s, 6H, -OC*H$_3$*). ^{19}F NMR (376 MHz, *CDCl$_3$*) δ_F -166.73 (t, $^{3}J_{HF}$ =

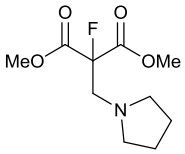
26.1 Hz). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ_C 11.62 (-NCH$_2$*C*H$_3$), 47.97 (-N*C*H$_2$CH$_3$), 52.99 (-O*C*H$_3$), 56.38 (d, $^2J_{CF}$ = 18.7 Hz, -CF-*C*H$_2$), 97.27 (d, $^1J_{CF}$ = 200.0 Hz, -*C*F), 165.82 (d, $^2J_{CF}$ = 26.3 Hz, -*C*(O)OCH$_3$). MS (ESI) m/z 236.14 ([M+H]$^+$, 100%), 178.08 ([M-C$_2$H$_3$O$_2^{\bullet}$+2H]$^+$, 64.1%), 122.04 (43.1%), 86.02 ([M-C$_5$H$_6$FO$_4^{\bullet}$]$^+$, 36.9%). HRMS (ESI) m/z calcd for [M+H]$^+$ C$_{10}$H$_{19}$FNO$_4$ 236.1298; found 236.1299.

Dimethyl-2-((diisopropylamino)methyl)-2-fluoromalonate 6b



^{1}H NMR (400 MHz, *CDCl$_3$*) δ_H 0.95 (d, *J* = 6.7 Hz, 6H, -CH(C*H$_3$*)$_2$), 2.97 – 3.13 (m, 1H, -CF-C*H$_2$*), 3.29 (m, 1H, -N-C*H*), 3.80 (s, 3H, -OC*H$_3$*).^{19}F NMR (376 MHz, *CDCl$_3$*) δ_F -163.14 (t, *J* = 26.7 Hz). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ_C 20.62 (-CH(*C*H$_3$)$_2$), 48.42 (-N-*C*H), 49.51 (d, $^2J_{CF}$ = 19.1 Hz, -CF-*C*H$_2$), 52.96 (-C(O)O*C*H$_3$), 97.98 (d, $^1J_{CF}$ = 199.3 Hz, -*C*F), 166.05 (d, $^2J_{CF}$ = 26.4 Hz, -*C*(O)OCH$_3$). MS (ESI) m/z 102.26 ([M-C$_6$H$_8$FO$_4^{\bullet}$]$^+$, 100%), 114.10 ([M-C$_5$H$_6$FO$_4^{\bullet}$]$^+$, 49.6%), 264.29 ([M+H]$^+$, 68.5%). HRMS (ESI) m/z calcd for [M+H]$^+$ C$_{12}$H$_{23}$FNO$_4$ 264.1620; found 264.1611.

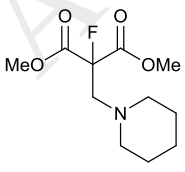
Dimethyl-2-(pyrrolidin-1-methyl)-2-fluoromalonate 6c



^{1}H NMR (400 MHz, *CDCl$_3$*) δ_H 1.63 – 1.74 (m, 4H, C*H$_2$*), 2.54 – 2.66 (m, 4H, -NC*H$_2$*), 3.24 (d, $^3J_{HF}$ = 26.6 Hz, 2H, -CF-C*H$_2$*), 3.81 (s, 6H,–C(O)OC*H$_3$*). ^{19}F NMR (376 MHz, *CDCl$_3$*) δ_F -166.92 (t, *J* = 26.7 Hz). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ_C 23.89 (-NCH$_2$*C*H$_2$), 53.

18 (-C(O)O*C*H$_3$), 55.26 (-NCH$_2$), 58.67 (d, $^2J_{CF}$ = 19.5 Hz, -CF-*C*H$_2$), 96.43 (d, $^1J_{CF}$ = 200.4 Hz, -*C*F), 165.81 (d, $^2J_{CF}$ = 25.9 Hz, -*C*(O)OCH$_3$). MS (ESI) m/z 152.23 ([M-C$_5$H$_6$FO$_4^{\bullet}$]$^+$, 50.4%), 234.21 ([M+H]$^+$, 100%). HRMS (ESI) m/z calcd for [M+H]$^+$ C$_{10}$H$_{17}$FNO$_4$ 234.1142; found 234.1145.

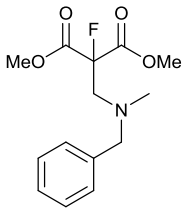
Dimethyl-2-(piperidin-1-methyl)-2-fluoromalonate 6d



^{1}H NMR (400 MHz, *CDCl$_3$*) δ_H 1.24-1.38 (m, 2H, C*H$_2$*), 1.44 (m, 4H, C*H$_2$*), 2.35 - 2.44 (m, 4H, NC*H$_2$*), 3.00 (d, $^3J_{HF}$ = 26.6 Hz, 2H, -CF-C*H$_2$*), 3.74 (s, 6H, -OC*H$_3$*).^{19}F NMR (376 MHz, *CDCl$_3$*) δ_F -165.65 (t, $^3J_{HF}$ = 26.6 Hz). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ 23.79 (*C*H$_2$), 26.17 (*C*H$_2$), 52.88 (-C(O)O*C*H$_3$), 55.62 (-NCH$_2$), 61.11 (d, $^2J_{CF}$ = 18.8 Hz, -CF-*C*H$_2$), 97.11 (d, $^1J_{CF}$ = 200.9 Hz, -*C*F), 165.71 (d, $^2J_{CF}$ = 26.1 Hz, -*C*(O)OCH$_3$). MS (ESI) m/z

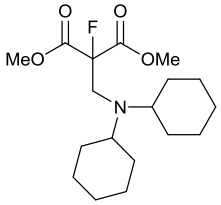
85.85 ([M-$C_6H_8FO_4^{\bullet}$+H]$^+$, 100%), 190.10 ([M-$C_2H_3O_2^{\bullet}$+H]$^+$, 95.7%), 248.15 ([M+H]$^+$, 73.6%). HRMS (ESI) m/z calcd for [M+H]$^+$ $C_{11}H_{19}FNO_4$ 248.1298; found 248.1296.

Dimethyl-2-((benzylmethylamino)methyl)-2-fluoromalonate 6e



^{1}H NMR (400 MHz, *CDCl$_3$*) δ_H 2.31 (s, 3H, -NC*H$_3$*), 3.31 (d, $^3J_{HF}$ = 25.9 Hz, 2H, -CF-C*H$_2$*), 3.68 (m, 2H, -N-C*H$_2$*), 3.85 (s, 6H, -OC*H$_3$*), 7.11 – 7.55 (m, 5H, ArH). ^{19}F NMR (376 MHz, *CDCl$_3$*) δ_F -166.08 (t, $^3J_{HF}$ = 25.9 Hz). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ_C 43.53 (-N*C*H$_3$), 53.22 (-C(O)O*C*H$_3$), 59.89 (d, $^2J_{CF}$ = 18.7 Hz, -CF-*C*H$_2$), 63.46 (-N-*C*H$_2$), 97.03 (d, $^1J_{CF}$ = 200.2 Hz, -*C*F), 126.76, 128.18, 128.90 (Ar), 138.73 (Ar), 165.73 (d, $^2J_{CF}$ = 26.1 Hz, -*C*(O)OCH$_3$). MS (ESI) m/z 122.09 ([M-$C_6H_8FO_4^{\bullet}$+2H]$^+$, 100%), 90.98 ([M-$C_7H_{11}FNO_4^{\bullet}$]$^+$, 65.3%), 284.12 ([M+H]$^+$, 44.8%). HRMS (ESI) m/z calcd for [M+H]$^+$ $C_{14}H_{19}FNO_4$ 284.1298; found 284.1301.

Dimethyl-2-((dicyclohexylamino)methyl)-2-fluoromalonate 6f



^{1}H NMR (400 MHz, *CDCl$_3$*) δ_H 0.96 –1.98 (m) (20H, C*H$_2$*), 2.42 – 2.70 (m, 2H, –N-C*H*), 3.39 (d, $^3J_{HF}$ = 26.4 Hz, 2H, -CF-C*H$_2$*), 3.79 (s, 6H, -OC*H$_3$*).^{19}F NMR (376 MHz, *CDCl$_3$*) δ_F -166.39 (t, $^3J_{HF}$ = 21.9 Hz). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ_C 25.23 (*C*H$_2$), 28.4 (*C*H$_2$), 33.57 (N*C*H$_2$), 52.96 (N-*C*H), 53.46 (-C(O)O*C*H$_3$), 63.47 (d, $^2J_{CF}$ = 21.5 Hz, -CF-*C*H$_2$), 95.59 (d, $^1J_{CF}$ = 199.9 Hz, -*C*F), 165.28 (d, $^2J_{CF}$ = 25.5 Hz, -*C*(O)OCH$_3$). MS (ESI) m/z 182.31 ([$C_{12}H_{22}N^{\bullet}$+H]$^+$, 100%), 194.34 ([M-$C_5H_6FO_4^{\bullet}$]$^+$, 79.3%), 344.20 ([M+H]$^+$,15.8%). HRMS (ESI) m/z calcd for [M+H]$^+$ $C_{18}H_{31}FNO_4$ 344.2237, found 344.2247.

Mannich-type reaction by semi-continuous flow two-step process general procedure

After purging the continuous flow reactor apparatus described previously [18] with nitrogen, a 10% mixture of fluorine in nitrogen (v.v^{-1}) (11 mmol, 1.1 eq.) was passed through the first flow reactor via Input 1 at a prescribed flow rate that was controlled by a gas mass flow controller (Brooks Instruments). The flow reactor was cooled by an external cryostat to 0-5°C. The ethyl-acetoacetate solution in acetonitrile (10 mL,

1 mmol/mL) was injected by a HPLC pump into the flow reactor channel at a prescribed flow rate through Input 2 (5 mL/h). The gas-liquid flow stream was passed through the first reactor and the product mixture was collected in a three-neck round-bottomed flask.

This collected mixture was directly injected by a HPLC pump into the second flow reactor at a prescribed flow rate (5 mL/h). Formaldehyde (15 mmol) and the amine 3 (17 mmol) were mixed together in acetonitrile for 2 h at rt and then injected by HPLC pump into the second flow reactor channel at a prescribed flow rate through the corresponding substrate Input via a T-piece. The molar ratio of fluorinated ethylacetoacetate:formaldehyde:amine was *ca.* 1:1.5:1.7. The liquid flow stream was passed through the second reactor and the product mixture was collected in a second two-neck round-bottomed flask. All flow streams were passed through the reactor and the product mixture was collected in a two-neck round-bottom flask. The collected mixture was then poured into water, extracted with dichloromethane (3 × 50 mL) and washed with brine (20 mL) and water (20 mL). The combined extracts were then dried ($MgSO_4$), filtered and the solvent evaporated to give a yellow oil, which was purified by micro-distillation or column chromatography on silica gel using hexane/ethyl acetate as eluent system when appropriate.

Acknowledgements

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References

[1]. a) K. Muller, C. Faeh, F. Diederich, Science 317 (2007)1881-1886; b) I. Ojima, (Ed), Fluorine in Medicinal Chemistry and Chemical Biology. Wiley-Blackwell, Oxford, 2009; c) S. Purser, P.R. Moore, S. Swallow, V. Gouverneur, Chem. Soc. Rev. 37 (2008) 320-330; d) C. Isanbor, D. O'Hagan, J. Fluorine Chem. 127 (2006) 303-319; e) K.L. Kirk, J. Fluorine Chem. 127 (2006) 1013-1029.

[2]. a) FY 2011 Innovative Drug Approvals. http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm276385.htm ; b) E.A. Ilardi, E. Vitaku, J.T. Njardarson, J. Med. Chem. 57 (2014) 2832-2842; c) F. Lovering, J. Bikker, C. Humblet, J. Med. Chem. 52 (2009) 6752 – 6757; d) N.J. Willis, C.A. Fisher, C.M. Alder, A. Harsanyi, L. Shukla, J.P. Adams, G. Sandford, Green Chem. 18 (2016) 1313-1318.

[3]. J.M. Percy, Top. Curr. Chem. 199 (1997) 131-195.

[4]. a) R. D. Chambers, J. Hutchinson, J. Fluorine Chem. 92 (1998) 45-51; b) R.D. Chambers, M.A. Fox, D. Holling, T. Nakano, T. Okazoe, G. Sandford, Chem. Eng. Tech, 28 (2005) 344-352; c) A. Harsanyi, G. Sandford, Green Chem. 17 (2015) 3000-3009.

[5]. R.D. Chambers, M.P. Greenhall, J. Hutchinson, Tetrahedron 52 (1996)1-8.

[6]. M. Butters, J. Ebbs, S.P. Green, J. MacRae, M.C. Morland, C.W. Murtiashaw, A.J. Pettman, Org. Proc. Res. Dev. 5 (2001) 28-35.

[7]. A. Harsanyi, G. Sandford, Org. Proc. Res. Dev. 18 (2014) 981-992.

[8]. a) A. Harsanyi, G. Sandford, D.S. Yufit, J.A.K. Howard, Bielstein J. Org. Chem. 10 (2014) 1213–1219; b) C.A. Fisher, A. Harsanyi, G. Sandford, D.S. Yufit, J.A.K. Howard, CHIMIA 68 (2014) 425-429.

[9]. A. Strecker, Liebigs Ann. Chem. 75 (1850) 27-45.

[10]. a) O. Kappe, Acc. Chem. Res. 33 (2000) 879-888; b) S. K. Burr, S. F. Martin, Tetrahedron 57 (2001) 3221-3242; c) S. F. Martin, Acc. Chem. Res. 35 (2002) 895-904.

[11] a) Y. K. Kang, D. Y. Kim, Tetrahedron Lett. 52 (2011) 2356-2358; b) S. J. Yoon, Y. K. Kang, D. Y. Kim, Synlett 3 (2011) 420-424; c) Y. Zhao, Y. Pan, H. Liu, Y. Yang, Z. Jiang, C. H. Tan, Chem. Eur. J. 17 (2011) 3571-3574; d) S. T. Kadam, S. S. Kim, Tetrahedron 66 (2010) 5647-5652; e) J. H. Lee, D. Y. Kim, Synthesis 11 (2010) 1860-1864; f) S. Fustero, F. Mojarrad, M. D. P. Carrion, J. F. Sanz-Cervera, J. L. Acena, Eur. J. Org. Chem. 2009, 5208-5214; g) X. Han, J. Kwiatkowski, F. Xue, K. W. Huang, Y. Lu, Angew. Chem. Int. Ed. 48 (2009) 7604-7607; h) S. Mizuta, N. Shibata, Y. Goto, T. Furukawa, S. Nakamura, T.

Toru, J. Am. Chem. Soc. 129 (2007) 6394-6395; i) M. Lu, Y. Lu, P. K. M. Tan, Q. Y. Lau, G. Zhong, Synlett 4 (2011) 477-480.

[12] G. K. Prakash, L. Gurung, P. V. Jog, S. Tanaka, T. E. Thomas, N. Gansh, R. Haiges, T. Mathew, G. Olah, Chem. Eur. J. 19 (2013) 3579.

[13] K. Pham, X. Huang, W. Zhang, Tetrahedron Lett. 56 (2015)1998-2000.

[14] a) K.G. Gadamasetti, Process Chemistry in the Pharmaceutical Industry Marcel Dekker, New York, 1999; b) W. Ehrfeld, V. Hessel, H. Lowe, Microreactors. New Technology for Modern Chemistry; Wiley-VCH: New York, 2000; c) C. Wiles, P. Watts, Microreaction Technology in Organic Synthesis; CRC Press: Boca Raton, 2011.

[15] A. Odedra, P. H. Seeberger, Angew. Chem. Int. Ed. 48 (2009) 2699-2702.

[16] a) C. Ayats, A. H. Henseler, E. Dibello, M. A. Pericàs, ACS Catal. 4 (2014) 3027-3033; b) E. Alza, C. Rodriguez-Escrich, S. Sayalero, A. Bastero, M. A. Pericàs, Chem. Eur. J. 15 (2009) 10167-10172; c) R. Martìn-Rapùn, S. Sayalero, M. A. Pericàs, Green Chem. 15 (2013) 3295-3301.

[17] C.B. McPake, G. Sandford, Org. Proc. Res. Dev. 16 (2012) 844-851.

[18] A. Harsanyi, A. Conte, L. Pichon, A. Rabion, S. Grenier, G. Sandford, Org. Proc. Res. Dev. 21 (2017) 273-276.

[19] J.R. Breen, G. Sandford, D.S. Yufit, J.A. K. Howard, J. Fray, B. Patel, Beilstein. J. Org. Chem. 7 (2011) 1048–1054.

Figures

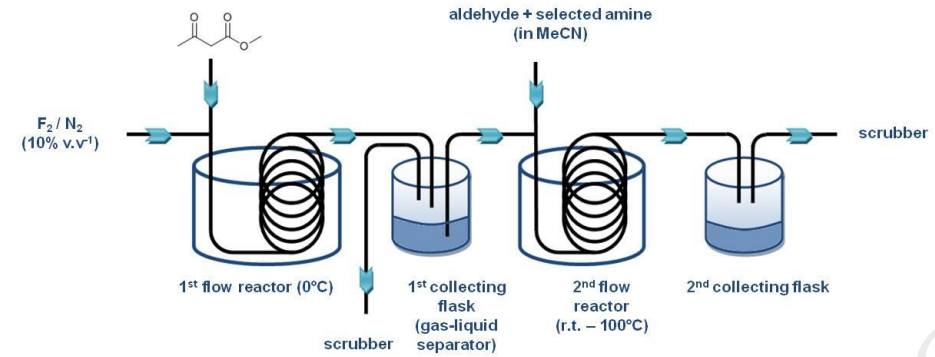
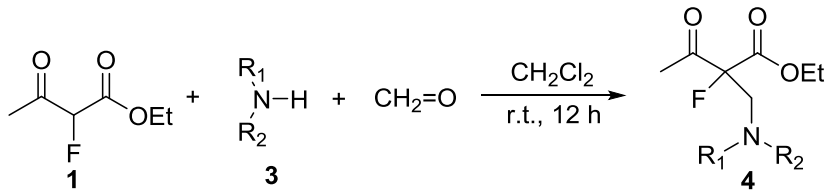
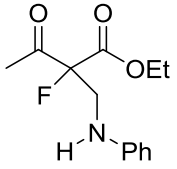
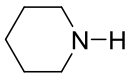
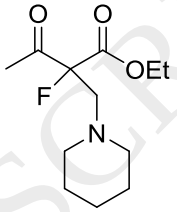
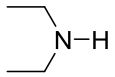
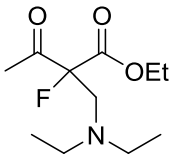
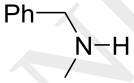
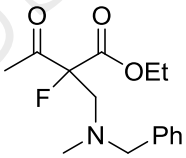
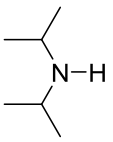
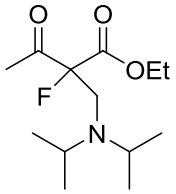
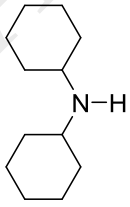
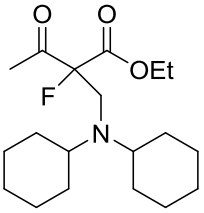
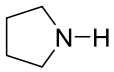
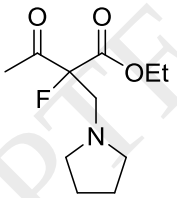


Figure 1. Schematic diagram of semi-continuous flow process (top); coiled stainless steel flow reactors (bottom)

Tables

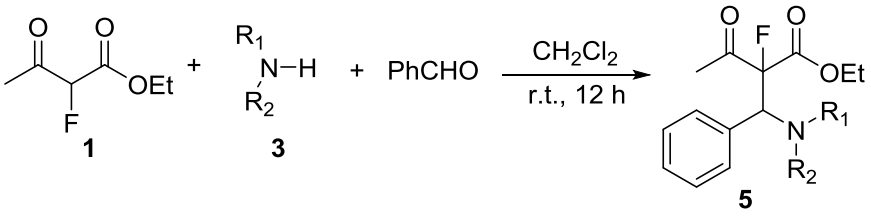
Table 1 Three-component Mannich-type reaction of 2-fluoro-ethylacetoacetate **1,** formaldehyde and amine **3**

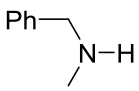
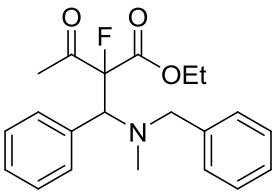
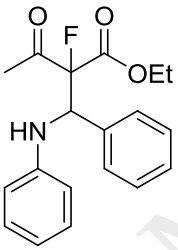
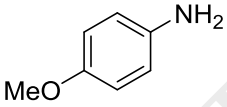
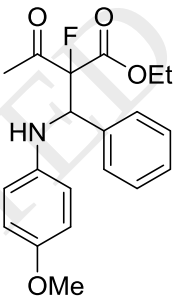


Amine **3**	Product **4**	Yield[a]	Amine **3**	Product **4**	Yield[a]
Ph-NH_2		**4a**, 79 [b]			**4e**, 98 (97) [d]
		**4b**, 98 (75 [c]) (quant.) [d]			**4f**, 95 (98) [d]
		**4c**, 90 (95) [d]			**4g**, 92
		**4d**, 98 (98) [d]			

[a] Isolated yield
[b] Reaction at reflux temperature
[c] Reaction in acetonitrile
[d] Reaction using NaH as base

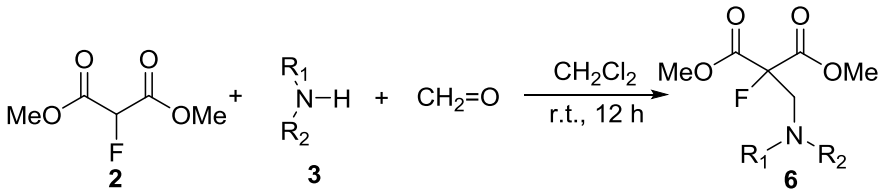
Table 2 Three-component Mannich-type reaction of 2-fluoro-ethylacetoacetate **1,** benzaldehyde and amine **3**

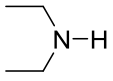
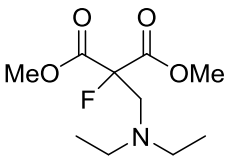
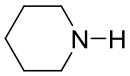
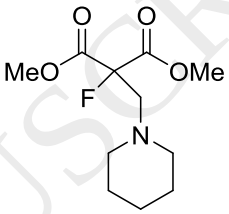
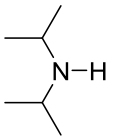
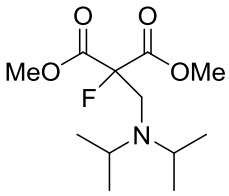
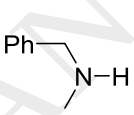
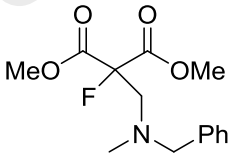
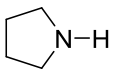
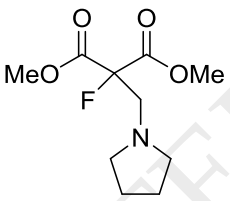
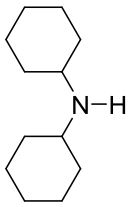
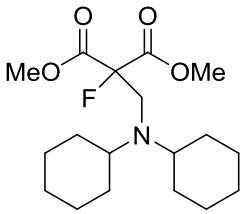


Amine **3**	Product **5**	Yield
		**5a**, 79
Ph-NH_2		**5b**, 84
		**5c**, 92

The synthetic conditions developed above were then applied to reactions between dimethyl 2-fluoro-malonate ester **2** and a range of amines **3** (Table **3**), resulting in analogous products **6** but in lower yield reflecting the lower nucleophilicity of the diester substrate.

Table 3 Three-component Mannich-type reaction of diethyl 2-fluoro-malonate ester **2,** formaldehyde and amine **3**

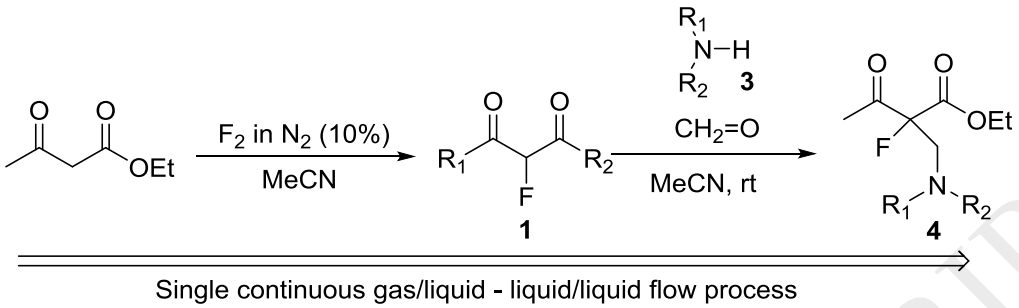


Amine **3**	Product **6**	Yield[a]	Amine **3**	Product **6**	Yield[a]
		**6a**, 98			**6d**, 97 (97 [b])
		**6b**, 71 (75 [b])			**6e,** 95 (94 [b])
		**6c,** 78 (80 [b])			**6f**, 80

[a] Isolated yield

b Reaction carried out using NaH

Table 4 Synthesis of β-fluoro(dicarbonyl)alkylamines **4** from ethylacetoacetate, amines **3** and formaldehyde by semi-continuous flow process



Single continuous gas/liquid - liquid/liquid flow process

R_1	R_2	Product	Yield [%][a]
CH_2CH_3	CH_2CH_3	**4b**	71
^{i}Pr	^{i}Pr	**4c**	43
-$(CH_2)_4$-	-	**4d**	55
-$(CH_2)_5$-	-	**4e**	59
Bn	CH_3	**4f**	67

[a] isolated yield