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FULL PAPER

α-Fluorotricarbonyl derivatives as versatile fluorinated building blocks: synthesis of fluoro-acetophenone, fluoro-ketoester and fluoro-pyran-4-one derivatives

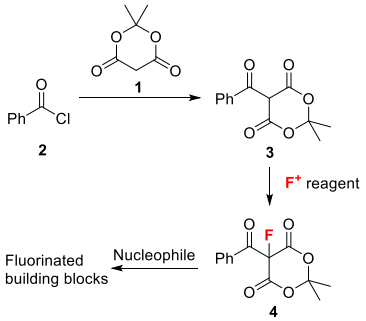
Antal Harsanyi, Anne Lückener, Hedvig Pasztor, Zahide Yilmaz, Lawrence Tam, Dmitry S. Yufit and Graham Sandford*

Abstract: Fluorinated acyl-Meldrum's acid derivatives were synthesised by electrophilic fluorination of appropriate phenacyl Meldrum's acid substrates using Selectfluor. Reactions with water, ethanol, Grignard and alkynyl lithium reagents gave rise to the corresponding fluoro-acetophenone, -1,3-ketoester, -1,3-diketone and -pyran-4-one products respectively from the same selectively fluorinated scaffold in one-step procedures.

Introduction

The development of robust and scalable methods for the synthesis of polyfunctional aliphatic fluorinated building blocks continues to be of interest due, in part, to the increasing number of new chemical entities bearing fluorine atoms at sp_3 carbon sites that are entering pharmaceutical, agrochemical and materials company product pipelines[1] Consequently, methodology for fluorination at sp^3 sites utilising a variety of nucleophilic and electrophilic fluorinating agents continues to be developed to meet the needs for exploring new fluorinated chemical space.[2] Alternatively, the construction of polyfunctional fluorinated aliphatic systems by early stage fluorination and subsequent elaboration into more structurally complex systems offers a complementary approach. Consequently, many fluorine containing building blocks have been assessed in a variety of reaction processes and, in particular, the chemistry of a range of fluorinated diesters,[3] amides, ketones and aldehydes, for example, has been established.[4] However, the availability of a sufficiently wide range of fluorinated building blocks with established robust reactivity profiles can be a significant bottleneck in the synthesis of polyfunctional fluoroaliphatic systems. Thus, there remains a requirement for the development of synthetic routes to multi-functional fluorinated aliphatic building blocks for applications in diversity oriented synthesis as part of drug discovery programmes.

While the chemistry of synthetically versatile 2-fluoro-1,3-dicarbonyl derivatives continues to develop,[5] reports on the preparation and synthetic utility of related α-fluorotricarbonyl compounds are very rare in the literature despite their potential utility as versatile fluorinated building blocks. Tricarbonyl systems can be accessed readily, for example, acylation of Meldrum's acid gives corresponding α-tricarbonyl derivatives by either condensation with carboxylic acids using appropriate coupling reagents or from the corresponding mixed anhydride or acid chloride.[6] However, despite the use of readily available acyl Meldrum's acid derivatives in organic synthesis, there are very few reports in the literature concerning the synthesis and use of corresponding α-fluoro-derivatives. Formation of fluoro-tricarbonyl systems by double acylation of ethyl fluoroacetate[7] and fluorination of tricarbonyl compounds using perchloryl fluoride[8] have been reported previously. In addition, Kim and co-workers showed that triethyl 2-fluorophosphonoacetate can be acylated twice using an $MgCl_2$-Et_3N reagent system to afford 2-fluoro-diketo-ester derivatives.[9]



Scheme 1. Strategy for the synthesis and use of α-fluorotricarbonyl compounds derived from Meldrum's acid.

In this paper, we report the synthesis of α-fluoro-acyl Meldrum's acid derivatives using Selectfluor™ to gain access to potentially useful polyfunctional fluorinated tricarbonyl systems and, in proof-of-concept studies, show how these scaffolds may be used to

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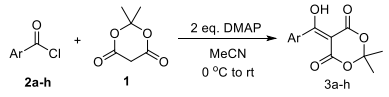
provide access to fluoro-acetophenone, -ketoester and -pyran-4-one derivatives by reaction with appropriate nucleophiles following a synthetic strategy outlined in Scheme 1. Neither the synthesis nor reactivity of fluorinated acyl Meldrum's acid derivatives have been described previously.

Results and Discussion

Syntheses of appropriate acyl Meldrum's acid derivatives **3** were carried out by acylation of Meldrum's acid **1** using a variety of aromatic acid chloride substrates **2** in acetonitrile in the presence of DMAP at ambient temperature by adapting a literature procedure.[10] After the reaction had reached completion, aqueous hydrochloric acid was added to dissolve the precipitated DMAP hydrochloride salt and acetonitrile was evaporated from the mixture under reduced pressure to precipitate the desired tricarbonyl product which was dried and recrystallized from acetone if required (Table 1). X-ray crystallography confirmed the structures of **3a** and **3g** showing that the systems exist as the enol forms in the solid state (Figure 1) with typical enol intra-molecular OH…O(carbonyl) hydrogen bonds.

Table 1. Synthesis of acyl Meldrum's acid derivatives ***3***.



Acid Chloride **2**	Product **3**, yield	Acid Chloride **2**	Product **3**, yield
2a	**3a**, 90 %	**2e**	**3e**, 85 %
2b	**3b**, 60 %	**2f**	**3f, 91 %**
2c	**3c**, 79 %	**2g**	**3g**, 74 %
2d	**3d**, 59 %	**2h**	**3h, 78 %**

Fluorinations of acyl Meldrum's acid derivatives **3** were carried out using electrophilic fluorinating reagent Selectfluor™ in acetonitrile at ambient temperature over 16 h (Table 2) after which ^{19}F NMR spectroscopic analysis of the reaction mixture confirmed full conversion to the desired product. Isolation of the desired α-fluoro-tricarbonyl products were achieved by selective dissolution of the crude residue into ethyl acetate and evaporation of the solvent after filtration from Selectfluor™ salt residues. When required, the crude product was further purified by dissolving in a small volume of dichloromethane/hexane and, after cooling at 0-5 °C, the desired fluorotricarbonyl products precipitated in good yield as fine powders. Crystalline products for diffraction studies were obtained by further recrystallisation from acetone.

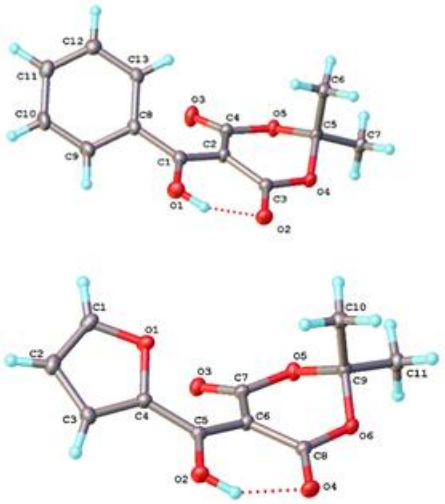
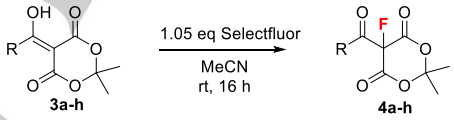


Figure 1. Molecular structures of **3a** and **3g**

Table 2. Fluorination of acyl Meldrum's acid derivatives.



Product **4**, yield	Product **4**, yield
4a, 74 %	**4e, 45 %**
4b, 70 %	**4f**, 75 %
4c, 64 %	**4g**, 92 %
4d, 75 %	**4h, 93 %**

Under these reaction conditions, competing electrophilic fluorination of the aromatic ring was not observed, even in the case of the electron rich thiophene and furan derivatives and the

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products were found to be stable for a long time (over a month) in a refrigerator if moisture was excluded.

X-ray crystallographic analysis of fluorinated acyl Meldrum's acid derivatives **4a,c,d** (Figure 2) showed that the cyclohexane ring of these compounds adopts a distorted boat conformation where the torsion angle between the fluorine atom and the C=O oxygen atoms of the ring is approximately 30°. This conformation is further stabilized by short intra-molecular CH...O(carbonyl) contacts (2.4-2.47Å) which can be regarded as weak hydrogen bonds. The difference between the two methyl groups can also be observed in the solution phase by ^{1}H and ^{13}C NMR spectroscopy where separate chemical shifts corresponding to the axial and equatorial environments are observed (for example, **3a**: 1.92 ppm and 1.86 ppm).

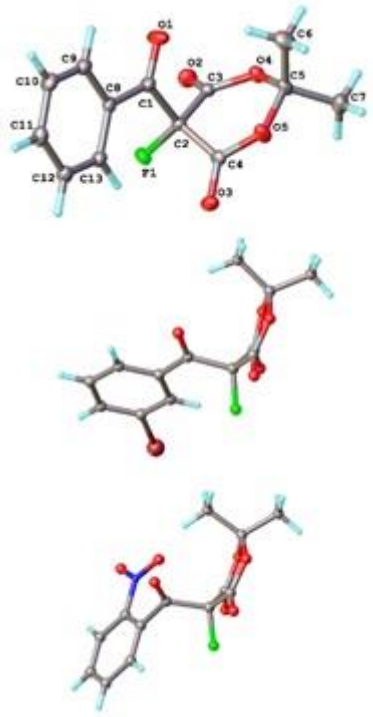
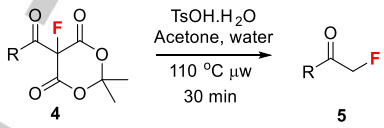


Figure 2. Distorted boat conformation of fluorinated Meldrum's acid derivatives **4a,c,d**

With a range of α-fluorotricarbonyl derivatives **4** in hand we began to explore reactions between these systems and some representative nucleophiles. Initially, a range of acid catalysed hydrolysis conditions were screened on 1 mmol scale to develop the hydrolysis reaction of **4a** to form the corresponding fluoro-acetophenone derivative 5a (see Supporting Information, Table SI1). The screening experiments (Table SI1) revealed that *p*-toluenesulfonic acid monohydrate was the most suitable reagent combination. Additional water improved the selectivity and conversion of the reaction, but more than 0.1 mL of water per mmol of starting material did not have any further benefit. After purification by column chromatography, 2-fluoroacetophenone **5a** was isolated in 56% yield. Attack by water at the more electrophilic ester functionality of the α-fluorotricarbonyl substrates leads to decarboxylation to the fluoracetophenone system. Of course, fluoroacetophenones may be synthesised by a variety of methods including fluorination of appropriate enolate systems by Selectfluor[11] but, here, the concept of selective reactions of nucleophiles with α-fluorotricarbonyl derivatives was established.

Subsequently, the most effective hydrolysis reaction conditions were applied to a range of aromatic and heteroaromatic fluorinated Meldrum's acid derivatives **4** to give fluoroacetophenone derivatives **5** in good yield after flash column chromatography (Table 3). The higher yield obtained in the synthesis of **5d** suggests that an *ortho* substituent capable of further activating the system towards nucleophilic attack can improve the selectivity of the decarboxylation. The molecular structures of **5a** and **5d** were confirmed by X-ray crystallography (Figure 3). The presence of an *ortho*-nitro-substituent results in almost perpendicular orientation of the carbonyl group relative to the aromatic ring in **5d**.

Table 3. Synthesis of α-fluoroacetophenone derivatives **5**



Product **5**, yield
5a, 56 %
5f, 41 %
5b, 62 %
5g, 51 %
5c, 35 %
5h, 73 %
5d, 89 %

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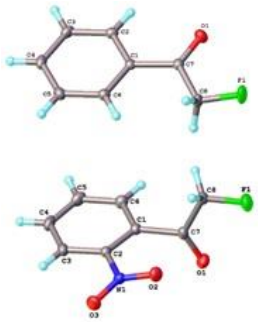
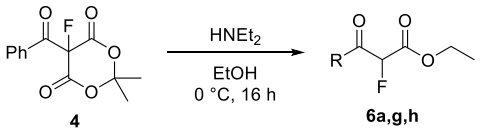


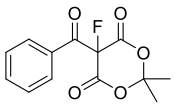
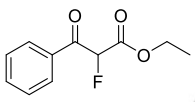
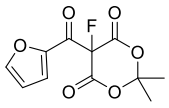
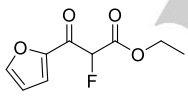
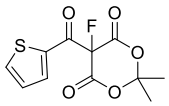
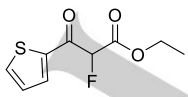
Figure 3. Molecular structure of fluoroacetophenones **5a** and **5d**

With model reactions between fluorotricarbonyl substrates **4** and water as the nucleophile established, reactions of fluoro-tricarbonyl derivatives with ethoxide were carried out to access the corresponding α-fluoro-ketoesters. Treating compound **4 a,g,h** in ethanol in basic conditions (Et_2NH) at 0 °C for 6 h afforded the desired products **6a,g,h** in excellent yield without any further purification required (Table 4).

Table 4: Synthesis of α-fluoro-β-ketoester derivatives **6**

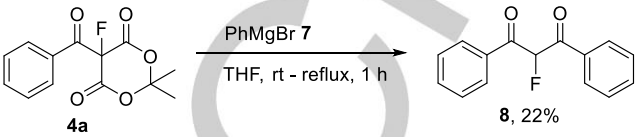


4 **6a,g,h**

4	6
 **4a**	 **6a** 94%
 **4g**	 **6g,** 86%
 **4h**	 **6h,** 87%

Thus, reactions of α-fluoro-tricarbonyl derivatives can lead to highly useful fluoroketoester building blocks upon reaction with ethanol in basic conditions, providing alternative synthetic routes to fluorination of ketoesters by fluorine gas[12] and Selectfluor[13] Fluorination of β-ketoesters by fluorine gas is effective[12] but can lead to difluorination at the enolic site and unselective fluorination, particularly on electron rich aromatic substituents such as the furan and thiophene moieties, in **6g,h**.We next studied reactions of appropriate carbon centred nucleophiles. Phenylmagnesium bromide **7** was formed in dry THF at r.t. from bromobenzene and magnesium turnings and added to **4a** and the reaction mixture that was heated at reflux for 1 h. Numerous unidentified side products were formed during this reaction as observed by ^{19}F NMR of the product mixture but purification via column chromatography and recrystallization gave the desired 2-fluoro-1,3-diphenylpropane-1,3-dione **8** albeit in low yield (Scheme 2).

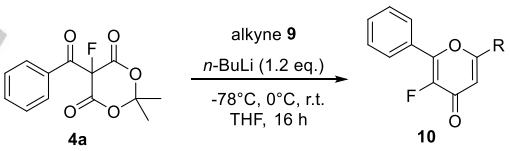
Scheme 2. Reaction of **4a** with Grignard reagent **7**



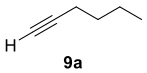
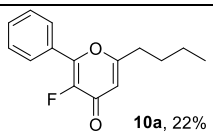
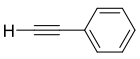
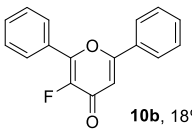
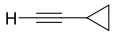
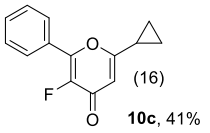
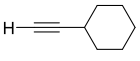
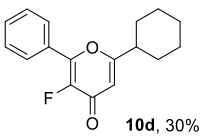
4a **8**, 22%

Analogous reactions of carbanions derived from terminal alkynes were next studied. Deprotonation of 1-hexyne **9a** using *n*-BuLi at -78°C in THF under an argon atmosphere followed by addition of **4a** and stirring of the reaction mixture overnight at room temperature gave a crude product which was purified by column chromatography and recrystallisation to give the unexpected 3-fluoro-4H-pyran-4-one derivative **10a** in moderate yield (22%) from a mixture of unidentified products (Table 5). Analogous syntheses of pyran-4-one derivatives **10b-d** were performed using ethynylbenzene **9b**, ethynylcyclopropane **9c** and ethynylcyclohexane **9d** substrates to give the fluoropyran-4-one products **10b-d** respectively The structures of pyranone products **10 a-d** were confirmed by X-ray crystallography (Figure 4).

Table 5. Synthesis of fluoro-pyran-4-one derivatives **10**



4a **10**

Alkyne **9**	Product **10**, yield
 **9a**	 **10a**, 22%
 **9b**	 **10b**, 18%
 **9c**	 (16) **10c**, 41%
 **9d**	 **10d**, 30%

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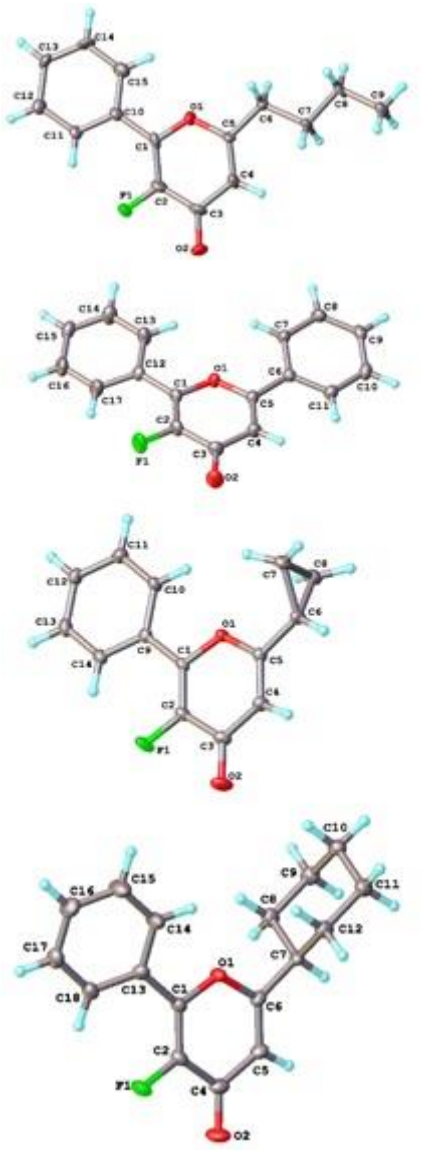
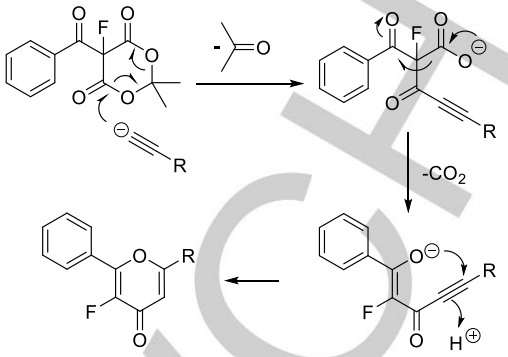


Figure 4. Molecular structures of fluoropyran-4-one derivatives **10a-d**

Carbanions formed by deprotonation of the alkynes attack an ester group of the Meldrum's acid moiety and, after elimination of acetone and decarboxylation, an enolate intermediate is formed. Intramolecular Michael-type addition forms the observed six-membered ring products (Scheme 3).



Scheme 3. Formation of **10**

While well-known 4H-pyran-2-one sub-units are found in various natural products[14] and generally synthesised by γ-acylation of 1,3-diketones with carboxylic ester substrates,[15] corresponding 2-fluoro-4H-pyran-2-ones have not been reported in the literature, despite their relatively simple structures.

Conclusions

In this paper, the synthesis and reactivity of fluorinated acyl Meldrum's acid derivatives with representative oxygen and carbon centred nucleophiles was described. Meldrum's acid was acylated and subsequent fluorination carried out using Selectfluor™ to provide access to the desired fluoro-tricarbonyl compounds in good yield. Reactions of the fluoro-tricarbonyl scaffolds with oxygen and carbon centred nucleophiles led to appropriate fluoro-acetophenone, -ketoester, -diketone and -pyran-4-one derivatives by simple processes. These proof-of-concept studies demonstrate that α-fluorotricarbonyl derivatives can be common substrates that allow access to a wide range of fluorinated aliphatic and heterocyclic building blocks.

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Experimental Section

5-Benzoyl-2,2-dimethyl-1,3-dioxane-4,6-dione **3a**

Meldrum's acid **1** (14.4 g, 100 mmol) and DMAP (24.4 g, 200 mmol) were dissolved in acetonitrile (250 mL) and cooled in ice-water. Benzoyl chloride **2a** (14.1 g, 100 mmol) was dissolved in acetonitrile (50 mL) and added dropwise over 40 min. The mixture was stirred for 16 h, then 1M HCl (200 mL) was added, the mixture stirred for 5 min (clear solution) and was concentrated to approximately 150 mL under vacuum. The precipitated product was filtered, washed with water (15 mL) and dried ($MgSO_4$) to give *5-benzoyl-2,2-dimethyl-1,3-dioxane-4,6-dione* **3a** (22.5 g, 90 %) as a yellow solid. Mp. 95-97 °C (with decomposition) (lit.[16] 103-104 °C, from acetone). IR (cm^{-1}): 2998, 1736, 1652. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.84 (s, 6H, CH_3), 7.47 (t, $^3J_{HH}$ 7.9, 2H, C**3**-H), 7.60 (tm, $^3J_{HH}$ 7.5, 1H, C**4**-H), 7.66 - 7.69 (m, 2H, C**2**-H), 15.47 (bs, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$)

δ 26.91 (CH_3), 91.06 (**C**(CH_3)$_2$), 106.11 (**C**=COH), 128.17 (C**3**-H), 129.58 (C**2**-H), 132.82 (C**1**-C), 133.44 (C**4**-H), 159.90 (C=**C**OH), 171.09 (**C**=O), 189.37 (**C**=O). m/z (ESI): 247 $[M-H]^-$, 207 (100 %, $[M-C_3H_5]^-$). HRMS (ESI) m/z calculated for $[M]^+$, $C_{13}H_{11}O_5$ requires: $[M]^+$, 247.0606; found 247.0605.

5-benzoyl-5-fluoro-2,2-dimethyl-1,3-dioxane-4,6-dione ***4a***

5-Benzoyl-2,2-dimethyl-1,3-dioxane-4,6-dione **3a** (2.48 g, 10.0 mmol) was dissolved in acetonitrile (50 mL) and Selectfluor (5.50 g, 15.5 mmol) was added to the mixture which was stirred at rt for 16 h. The reaction mixture was evaporated to dryness under vacuum, the solids suspended in ethyl acetate (50 mL), filtered and washed with ethyl acetate (30 mL). The ethyl acetate solution was evaporated under reduced pressure, the residue dissolved in dichloromethane (20 mL), hexane (60 mL) was added and the solution was concentrated at atmospheric pressure until solids started to appear (approximately 30 mL). After cooling at 4 ºC overnight the product was filtered and dried under vacuum to give *5-benzoyl-5-fluoro-2,2-dimethyl-1,3-dioxane-4,6-dione* ***4a*** (1.98 g, 74 %) as a yellow solid. Mp. 109-112 ºC. IR (cm^{-1}): 3071, 3019, 1797, 1756, 1675. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.86 (s, 3H, C**H$_3$**), 1.92 (s, 3H, C**H$_3$**), 7.53 (m, 2H, C**3**-H), 7.69 (m, 1H, C**4**-H), 8.22 (m, 2H, C**2**-H). ^{19}F NMR (376 MHz, $CDCl_3$) δ - 157.97 (t, $^5J_{HF}$ 1.9 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 27.67 (**C**H$_3$), 30.19 (**C**H$_3$), 92.13 (d, $^1J_{CF}$ 216 Hz, **C**-F), 109.43 (**C**(CH_3)$_2$), 128.90 (C**3**-H), 130.87 (d, $^4J_{CF}$ 6.1 Hz, C**2**-H), 132.06 (d, $^3J_{CF}$ 4.1 Hz, C**1**-C), 135.51 (C**4**-H), 159.15 (d, $^2J_{CF}$ 23.2, **C**=O), 188.16 (d, $^2J_{CF}$ 26.4, **C**=O). m/z (ASAP): 223 (27 %, $[M-C_3H_7]^+$); 165 (100 %, $[M-CH_3COCH_3-CO_2]^+$).

2-Fluoroacetophenone **5a**

5-Fluoro-5-(benzoyl)-2,2-dimethyl-1,3-dioxane-4,6-dione **4a** (1.07 g, 4.0 mmol) and *p*-toluenesulfonic acid monohydrate (0.76 g, 4.0 mmol) were dissolved in acetone (20 mL) in a microwave vial (25 mL). Water (0.4 mL) was added, the vial sealed and irradiated at 100 ºC for 30 min. After the mixture was allowed to cool to ambient temperature, the pressure was released by piercing the rubber septum with a needle. The mixture was evaporated to dryness, the residue dissolved in ethyl acetate (50 mL), washed with saturated $NaHCO_3$ solution (2x20 mL) and brine (20 mL). After drying (Na_2SO_4), the solvent was removed under reduced pressure and the product was purified by silica gel column chromatography (hexanes : ethyl acetate, 5 : 1) to afford *2-fluoroacetophenone* **5a** (0.31 g, 56 % yield) as a yellow oil. Rf.: 0.27 (hexanes : ethyl acetate, 5 : 1). IR (cm^{-1}): 3066, 2938, 1703, 1598. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.53 (d, $^2J_{HF}$ 46.9 Hz, 2H, CH_2F), 7.45 – 7.54 (m, 2H, C**3**-H), 7.58 – 7.66 (m, 1H, C**4**-H), 7.83 - 7.92 (m, 2H, C**2**-H). ^{19}F NMR (376 MHz, $CDCl_3$) δ - 231.44 (t, $^2J_{HF}$ 47.0 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 83.64 (d, $^1J_{CF}$ 182.6 Hz, **C**H$_2$F), 127.94 (d, $^4J_{CF}$ 2.6 Hz, C**2**-H), 129.03 (C**3**-H), 133.80 (C**1**-C), 134.24 (C**4**-H), 193.52 (d, $^2J_{CF}$ 15.5 Hz, **C**=O). m/z (ASAP): 139 (49 %, $[M+H]^+$). HRMS (ESI) m/z calculated for $[M+H]^+$, C_8H_8FO, 139.0559; found 139.0559.

Ethyl 2-fluoro-3-oxo-3-phenylpropanoate **6a**

5-Benzoyl-5-fluoro-2,2-dimethyl-1,3-dioxane-4,6-dione **4a** (1.00 g, 3.76 mmol) was dissolved in EtOH (10 mL) and the solution was cooled to 0 °C. Diethylamine (0.4 ml, 3.76 mmol) was added and the reaction was stirred at 0 °C for 16 h. The solvent was removed and the residue dissolved in DCM (30 mL). The organic layer was washed with sodium bicarbonate (10 mL) and brine (10 mL), dried and concentrated to give *ethyl 2-fluoro-3-oxo-3-phenylpropanoate* **6a**[17](745 mg, 94%) as a yellow oil without any further purification; IR (cm^{-1}): 1693, 1759, 1597, 1580. ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.00 (d, *J* 8.6 Hz, 2H, C**8**,**10**-H), 7.60 (t, *J* 7.5 Hz, 1H, C**6**-H), 7.46 (dd, *J* 8.4, 7.4 Hz, 2H, C**5**,**7**-H), 5.88 (d, *J* 48.7 Hz, 1H, C**1**-H), 4.25 (qd, *J* 7.1, 2.8 Hz, 2H, C**14**-H), 1.20 (t, *J* 7.2 Hz, 3H, C**15**-H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -190.4 (d, *J* 48.8 Hz). ^{13}C NMR (176 MHz, $CDCl_3$) δ 189.6 (d, $^2J_{CF}$ 20.0 Hz, C**11**-C), 164.9 (d, $^2J_{CF}$ 24.1 Hz, C**3**-C), 134.5 (C**6**-C), 133.4 (d, $^3J_{CF}$ 1.9 Hz, C**9**-C), 129.5 (d, $^4J_{CF}$ 3.3 Hz, C**8**,**10**-C), 128.8 (C**5**,**7**-C), 89.9 (d, $^1J_{CF}$ 197.1 Hz, C**1**-C), 62.65 (C**14**-C), 13.90 (C**15**-C); HRMS (ESI) m/z calculated for $[M-H]^-$ $C_{11}H_{10}O_3F^-$ 209.0614, found 209.0602.

2-Fluoro-1,3-diphenyl-1,3-propanedione **8**

Phenyl magnesium bromide was pre-formed by treating a mixture of Mg turnings (85 mg, 3.5 mmol) and a single Iodine crystal in dry THF (3 mL) at r.t. with bromobenzene (0.26 ml, 2.5 mmol), followed by stirring under argon during reflux for 1 h. After having cooled to r.t. the supernatant was removed and was then added dropwise to an ice/water bath cooled solution of 5-benzoyl-5-fluoro-2,2-dimethyl-1,3-dioxane-4,6-dione **4a** (300 mg, 1.13 mmol) in dry THF (1.5 mL) under an argon atmosphere and stirred overnight at r.t. Afterwards the mixture was stirred under reflux for approximately 30 min before being quenched with sat. aq. NH_4Cl (3 mL). The solution was diluted with a small amount of water and the aqueous layer extracted with Et_2O. The combined organic layers were dried ($MgSO_4$) and concentrated. The crude product was purified by column chromatography on silica gel (9:1 n-Hexane:EtOAc; Rf.: 0.2) and recrystallisation from DCM and *n*-hexane to give *2-fluoro-1,3-diphenyl-1,3-propanedione* **8**[18] (63 mg, 0.21 mmol, 22%) as a white solid. M. p. 66-67°C; M. p.[18] 66-67°C. IR (cm^{-1}): 3071, 1673. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 - 8.06 (m, 4H, ArH), 7.62 (ddt, *J* = 8.0, 6.9, 1.3 Hz, 2H, ArH), 7.52 - 7.45 (m, 4H, ArH), 6.54 (d, $^2J_{HF}$ 49.2 Hz, 1H, CHF). ^{19}F NMR (376 MHz, $CDCl_3$) δ -186.88 (d, $^1J_{CF}$ 49.2 Hz).^{13}C NMR (101 MHz, $CDCl_3$) δ 191.31 (d, $^2J_{CF}$ 20.2 Hz, C=O), 134.65 (s), 133.69 (d, $^5J_{CF}$ 1.9 Hz), 129.96 (d, $^4J_{CF}$ 3.5 Hz), 128.92 (s), 96.72 (d, $^1J_{CF}$ 198.9 Hz, CHF). HRMS (ASAP) m/z calculated for $[M+H]^+$ $C_{15}H_{12}FO_2$ 243.0816, found 243.0822.

6-Butyl-3-fluoro-2-phenyl-4H-pyran-4-one **10a**

A solution of 1-hexyne **9a** (0.13 mL, 1.13 mmol) in dry THF (1.5 mL) was cooled to -78 ºC under an argon atmosphere. *n*-BuLi (0.54 mL, 2.5 M in hexanes, 1.35 mmol) was added dropwise and the resulting solution stirred at -78 ºC for 1 h. A solution of 5-benzoyl-5-fluoro-2,2-dimethyl-1,3-dioxane-4,6-dione **4a** (300 mg, 1.13 mmol) in dry THF (2.5 mL) was added dropwise at 0 ºC and the solution was slowly warmed to r.t. while stirring overnight. After quenching with sat. aq. NH_4Cl (3 mL) the solution was diluted with water (5 mL) and the aqueous layer extracted with Et_2O. The combined organic layers were washed with brine before being dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography on silica gel (7:3 n-Hexane:EtOAc; Rf.: 0.2) and recrystallised from DCM and *n*-hexane, to give *6-butyl-3-fluoro-2-phenyl-4H-pyran-4-one* **10a** (62 mg, 22%) as a white solid. M. p. 39-40°C. IR (cm^{-1}): 3261, 2954, 2932, 1635. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.88 - 7.82 (m, 2H, C11,15-H), 7.55 - 7.49 (m, 3H, C12,13,14-H), 6.31 (dd, $^4J_{HF}$ 6.6, 1.3 Hz, 1H, C4-H), 2.63 (t, *J* 7.7 Hz, 2H, C6-H), 1.71 (p, *J* 7.6 Hz, 2H, C7-H), 1.56 - 1.29 (m, 2H, C8-H), 0.97 (tt, *J* 7.4, 1.1 Hz, 3H, C9-H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -158.88 (d, $^4J_{HF}$ 6.6 Hz).^{13}C NMR (176 MHz, $CDCl_3$) δ 172.40 (d, $^2J_{CF}$ 16.4 Hz,C3-C), 168.73 (C5-C), 150.79 (d, $^2J_{CF}$ 24.2 Hz, C1-C), 149.28 (d, $^1J_{CF}$ 253.5 Hz,C2-F), 131.29 (d, $^5J_{CF}$ 1.4 Hz, C12,14-C), 129.03 (C13-C), 128.65 (d, $^3J_{CF}$ 5.2 Hz, C10-C), 127.60 (d, $^4J_{CF}$ 7.6 Hz, C11,15-C), 114.21 (d, $^3J_{CF}$ 6.9 Hz, C4-C), 33.42(C6-C), 29.15(C7-C), 22.17(C8-C), 13.81(C9-C). HRMS (ASAP) m/z calculated for $[M+H]^+$ $C_{15}H_{16}FO_2^+$ 247.1129, found 247.1123.

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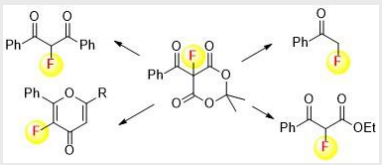
FULL PAPER

Fluorinated acyl-Meldrum's acid derivatives, synthesised by electrophilic fluorination react with nucleophiles to give fluoro-acetophenones, 2-fluoro-1,3-ketoester, 2-fluoro-1,3-diketone and fluoro-pyran-4-one products from the same fluorinated scaffold.



Fluorine Chemistry

*Antal Harsanyi, Anne Luckener, Hedvig Pasztor, Zahide Yilmaz, Lawrence Tam, Dmitry S. Yufit and Graham Sandford**

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α-Fluorotricarbonyl derivatives as versatile fluorinated building blocks: synthesis of fluoro-acetophenone, fluoro-ketoester and fluoro-pyran-4-one derivatives