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PAPER

One-pot fluorination followed by Michael addition or Robinson annulation for preparation of α-fluorinated carbonyl compounds†

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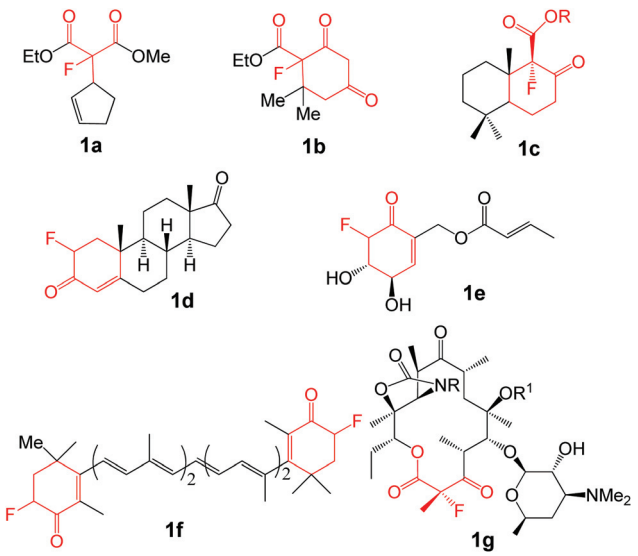
Fluorination followed by the Michael addition or Robinson annulation of 1,3-dicarbonyl compounds is introduced for the synthesis of acyclic and cyclic α-fluoro-β-ketoesters and α-fluoro-1,3-diketones. The decarboxylation step can also be added to the reaction sequence. High efficiency is achieved by the microwave heating and atom economic one-pot synthesis.

1. Introduction

Fluorination of organic compounds is a topic of current interest in medicinal chemistry.[1] Shown in Scheme 1 are α-fluorinated carbonyl molecules including intermediate **1a** for schizophrenia and anxiety agents,[2] intermediate **1b** for the human Kv1.1/Kvβ1 potassium channel inhibitor,[3] antimalarial candidate compound **1c**,[4] aromatase inhibitor **1d** as a promising candidate for the treatment of estrogen-dependent breast cancer,[5] intermediate **1e** for cytotoxic agent COTC,[6] retinal-protein bacteriorhodopsin **1f**,[7] and antibacterial erythromycin compound **1g**.[8] User friendly 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octanebis-(tetrafluoroborate) (Selectfluor™) and *N*-fluorobenzenesulfonimide (NSFI) are popular fluorination reagents.[9,10] Presented in this paper is a new reaction sequence including Selectfluor™-based fluorination followed by Michael addition or Robinson annulation reactions for the synthesis of α-fluoro-β-ketoesters or α-fluoro-1,3-diketones. It is a one-pot synthesis which combines the construction of molecular frameworks and the introduction of fluorine in a single operation. To the best of our knowledge, there is no such transformation reported in the literature. One-pot synthesis is an atom economic way to prepare molecules with substitution and skeleton diversities.[11] It eliminates waste generated from intermediates purification and is a favorable approach for green organic synthesis.[12]



Scheme 1

2. Results and discussion

Our first attempt of one-pot synthesis was to explore the fluorination and Michael addition reactions. This reaction sequence could generate fluorinated quaternary carbon existing in compounds **1a–c** and **1g** (Scheme 1). β-Ketoesters **2a**, **2b** and **2c** were selected for fluorination and then for Michael addition with chalcones **3a–g**. β-Ketoesters reacted with Selectfluor™ smoothly under microwave heating.[13] Addition of $CsCO_3$ and chalcones to the reaction mixture followed by additional microwave heating afforded **4a–i** in quantitative yields (Table 1).[14] Other than $CsCO_3$, bases such as KOH and Et_3N also worked well for the Michael addition reactions.

The success of one-pot fluorination and Michael addition encouraged us to extend the scope for Robinson annulation which could lead to cyclic compounds similar to **1b–f** shown in Scheme 1. Methyl acetoacetate **2d** and chalcone **3a** were used for the method development (Table 2). Different bases including hydroxides, carbonates, and amines were attempted for the Robinson annulation.[15] Reactions with NaOH or KOH gave **5a** in less than 20% yield. Reactions with amines such as Et_3N,

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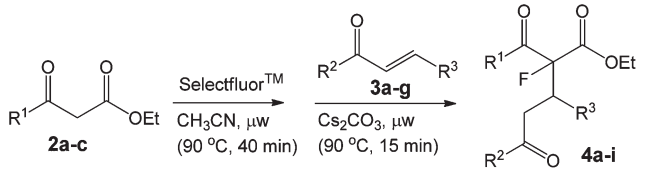
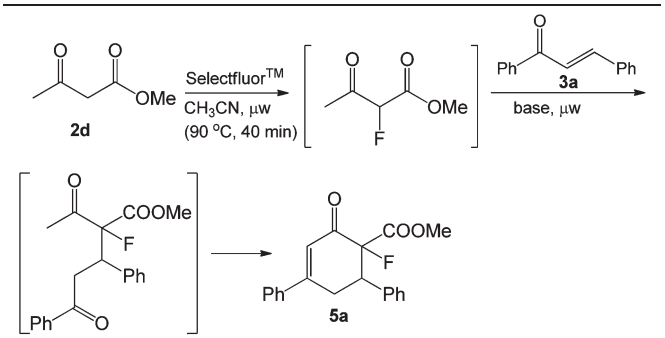
Table 1 One-pot fluorination and Michael addition[a]



Entry	R^1	R^2	R^3	Product	Yield[b] (%)	dr
1	Ph	Ph	Ph	**4a**	96 84[c] 79[d]	3/1
2	Ph	Ph	4-Me–Ph	**4b**	94	3/1
3	Ph	4-MeO–Ph	Ph	**4c**	92	4/1
4	Ph	4-Me–Ph	Ph	**4d**	96	3/1
5	Ph	Ph	4-NO_2–Ph	**4e**	90	3/1
6	4-Me–Ph	Ph	Ph	**4f**	95	3/1
7	4-NO_2–Ph	Ph	Ph	**4g**	97	3/1
8	Ph	4-MeO–Ph	4-MeO–Ph	**4h**	97	3/1
9	Ph	PhCH=CH	Ph	**4i**	93	4/1

[a] β-Ketoester (1 mmol), chalcone (1 mmol), Selectfluor™ (1 mmol), Cs_2CO_3 (0.5 equiv.), microwave heating at 90 °C for 15 min. [b] Isolated yield. [c] KOH (0.5 equiv.). [d] Et_3N (0.5 equiv.).

Table 2 Optimization of fluorination and Robinson annulation[a]



Entry	Base	Time (min)	Yield[b] (%)
1	NaOH	20	11
2	KOH	20	17
3	Na_2CO_3	30	38
4	K_2CO_3	30	61
5	Cs_2CO_3	30	89
6	Et_3N	60	24
7	DABCO	60	21
8	DMAP	60	37
9	DIPEA	60	19
10	Cs_2CO_3	30	39[c]
11	Cs_2CO_3	60	87
12	Cs_2CO_3	30	90[d]

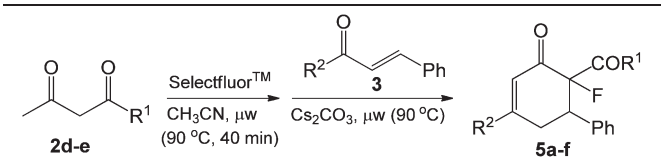
[a] **2d** (1 mmol), **3a** (1 mmol), Selectfluor™ (1 mmol), base 1 mmol, microwave heating at 90 °C. [b] Isolated yield, dr > 20/1. [c] NSFI was used. [d] 1.5 equiv. of base.

DABCO, DMAP and DIPEA also gave low yield. Cesium carbonate performed better than potassium and sodium carbonates and produced **5a** in 89% yield. A similar reaction using NSFI instead of Selectfluor™ gave the product in 39% yield (Table 2, entry 10). For the reaction with Selectfluor™, no significant improvement was observed by increasing the reaction time or amount of base (Table 2, entries 11 and 12).

Under the optimized condition of using Selectfluor™ as a fluorination agent and $CsCO_3$ as a base, reactions of β-ketoester **2d** and 1,3-diketone **2e** with α,β-unsaturated ketones gave the corresponding product **5a–f** in 80–89% isolated yield (Table 3). The Robinson annulation was further extended for the reaction of β-ketoester **2a** and α,β-unsaturated ketones **3h** and **3i** (Scheme 2). In this case, the acidic proton for the cyclization comes from the α,β-unsaturated ketones instead of the β-ketoesters shown in Table 3. The reaction condition was slightly modified by using $CsCO_3$ and sodium ethoxide as bases to promote the cyclization to give products **5g** and **5h** in 83% and 86% yields, respectively.

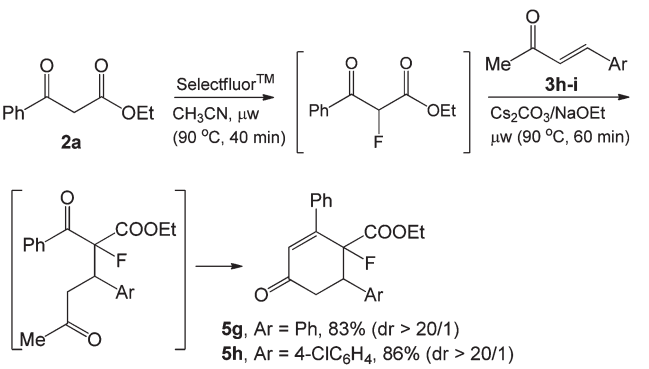
We thought it could be possible to perform decarboxylation at the end of fluorination and Robinson annulation reactions. It was found that decarboxylation could be easily achieved by heating the reaction mixture of Robinson annulation at 120 °C for 1 h. Thus, reactions of **2d** with **3a**, **3c**, and **3g** using Cs_2CO_3 and NaOEt as bases under microwave heating at 120 °C gave decarboxylation products **5i–k** in 81%, 87% and 84% yields, respectively (Scheme 3).

Table 3 One-pot fluorination and Robinson annulation[a]

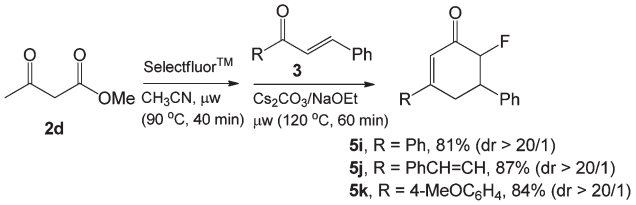


Entry	R^1	R^2	Product	Time (min)	Yield[b] (%)
1	OMe	Ph	**5a**	30	89
2	OMe	4-MeO–Ph	**5b**	30	87
3	OMe	PhCH=CH	**5c**	30	82
4	Me	Ph	**5d**	15	86
5	Me	4-MeO–Ph	**5e**	15	82
6	Me	PhCH=CH	**5f**	15	80

[a] **2d** or **2e** (1 mmol), α,β-unsaturated ketone (1 mmol), Selectfluor™ (1 mmol), Cs_2CO_3 (1 mmol), microwave heating at 90 °C. [b] Isolated yield, dr > 20/1.



Scheme 2



Scheme 3

3. Experimental

Chemicals and solvents were purchased from commercial sources and used as received. ^{1}H and ^{13}C NMR spectra were recorded on a 300 MHz Varian NMR spectrometer. The ratio of the diastereomers was determined by ^{1}H NMR. Only the peaks from the major diastereomer are given below. LC-MS was performed on the Agilent 2100 system with a C_{18} column for separation. Mass spectra were recorded in APCI (atmospheric pressure chemical ionization). Flash chromatography separations were performed on the Yamazen system with Agela silica gel columns.

Typical procedure for one-pot fluorination and Michael addition

The β-ketoester **2a** (192 mg, 1 mmol) was added to a solution of Selectfluor™ (354 mg, 1 mmol) in CH_3CN (2 mL). After irradiation in a Biotage Initiator microwave reactor at 90 °C for 40 min, the chalcone **3a** (208 mg, 1 mmol) and Cs_2CO_3 (50 mol %, 163 mg) were added and the mixture was then stirred at 90 °C for 15 min. EtOAc (10 mL) and H_2O (20 mL) were added. The organic layer was washed with aqueous HCl (2 M, 10 mL) and H_2O (10 mL), and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by flash column chromatography (6 : 1 hexane–EtOAc) to give fluorinated adduct **4a** (401 mg, 96%).

Ethyl 1,5-diphenyl-2-fluoro-3-phenyl-1,5-pentanedione-2-carboxylate (4a). White solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.27 (t, J = 7.2 Hz, 3H), 3.43 (m, 1H), 3.76 (m, 1H), 4.31 (q, J = 7.2 Hz, 2H), 4.80 (m, 1H), 7.11–7.69 (m, 13H), 7.90–8.12 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.7, 13.9, 39.6, 45.0, 45.2, 62.7, 63.2, 127.3, 127.8, 128.2, 128.3, 128.5, 128.6, 128.7, 129.1, 129.2, 129.6, 129.9, 130.0, 130.1, 133.1, 133.2, 133.3, 134.2, 172.4, 196.5, 200.3; ^{19}F NMR ($CFCl_3$, 300 MHz) δ 167.5, 167.6; MS (ACPI) m/z: 419.1 (M^+ + 1).

Ethyl 1,5-diphenyl-2-fluoro-3-(4′-methylphenyl)-1,5-pentanedione-2-carboxylate (4b). White solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.02 (t, J = 7.2 Hz, 3H), 2.27 (s, 3H), 3.25 (m, 1H), 3.62 (m, 1H), 3.97 (q, J = 7.2 Hz, 2H), 4.82 (m, 1H), 7.06–7.25 (m, 1H), 7.26–7.70 (m, 11H), 7.92 (d, 1H), 8.10 (d, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.7, 21.1, 39.9, 44.3, 44.6, 62.6, 128.1, 128.5, 128.7, 129.0, 129.4, 129.7, 130.0, 130.1, 133.0, 134.0, 134.2, 137.3, 172.1, 196.6, 200.2; ^{19}F NMR ($CFCl_3$, 300 MHz) δ 168.1, 168.3; MS (ACPI) m/z: 433.2 (M^+ + 1).

Ethyl 1-phenyl-2-fluoro-3-phenyl-5-(4′-methoxyphenyl)-1,5-pentanedione-2-carboxylate (4c). White solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.26 (t, J = 7.2 Hz, 3H), 3.32 (m, 1H), 3.63 (m, 1H), 4.29 (q, J = 7.2 Hz, 2H), 4.79 (m, 1H), 6.88 (m, 2H), 7.10–7.50 (m, 8H), 7.61–7.90 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.9, 39.1, 45.1, 55.5, 63.2, 113.6, 113.7, 127.3, 128.2, 128.6, 129.1, 129.2, 129.9, 130.4, 133.2, 195.0, 200.3, 215.9; ^{19}F NMR ($CFCl_3$, 300 MHz) δ 167.9, 168.0; MS (ACPI) m/z: 449.1 (M^+ + 1).

Ethyl 1-phenyl-2-fluoro-3-phenyl-5-(4′-methylphenyl)-1,5-pentanedione-2-carboxylate (4d). White solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.23 (t, J = 7.2 Hz, 3H), 2.38 (s, 3H), 3.39 (m, 1H), 3.73 (m, 1H), 4.33 (q, J = 7.2 Hz, 2H), 4.82 (m, 1H), 7.09–7.49 (m, 10H), 7.50–7.81 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.6, 13.9, 21.6, 39.3, 39.4, 39.7, 44.7, 45.0, 45.3, 62.6, 63.1, 127.2, 127.7, 128.1, 128.2, 128.6, 129.0, 129.1, 129.2, 129.6, 129.8, 129.9, 129.9, 130.0, 133.1, 134.1, 137.2, 137.7, 143.8, 144.0, 196.0, 199.4, 200.2, 215.8; ^{19}F NMR ($CFCl_3$, 300 MHz) δ 167.5, 167.9; MS (ACPI) m/z: 433.2 (M^+ + 1).

Ethyl 1,5-diphenyl-2-fluoro-3-(4′-nitrophenyl)-1,5-pentanedione-2-carboxylate (4e). Yellowish solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.26 (t, J = 7.2 Hz, 3H), 3.22 (m, 1H), 3.68 (m, 1H), 4.33 (q, J = 7.2 Hz, 2H), 4.89 (m, 1H), 7.35–7.68 (m, 9H), 7.76–7.90 (m, 2H), 8.04–8.18 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.8, 14.1, 39.3, 39.7, 63.0, 63.6, 117.3, 123.3, 123.4, 128.0, 128.5, 128.7, 128.8, 128.8, 129.3, 130.0, 130.1, 130.7, 130.9, 133.5, 134.0, 134.6, 163.8, 164.1, 195.8, 200.2, 212.5; ^{19}F NMR ($CFCl_3$, 300 MHz) δ 166.8, 167.7; MS (ACPI) m/z: 464.1 (M^+ + 1).

Ethyl 1-(4′-methylphenyl)-2-fluoro-3,5-diphenyl-1,5-pentanedione-2-carboxylate (4f). White solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.26 (t, J = 7.2 Hz, 3H), 2.34 (s, 3H), 3.38 (m, 1H), 3.75 (m, 1H), 4.30 (q, J = 7.2 Hz, 2H), 4.81 (m, 1H), 7.12–7.65 (m, 12H), 7.89 (d, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.9, 21.7, 39.6, 45.0, 63.1, 127.3, 128.0, 128.2, 128.3, 128.6, 129.0, 129.4, 129.9, 133.2, 196.1, 199.4, 200.2; ^{19}F NMR ($CFCl_3$, 300 MHz) δ 167.0, 167.2; MS (ACPI) m/z: 433.2 (M^+ + 1).

Ethyl 1-(4′-nitrophenyl)-2-fluoro-3,5-diphenyl-1,5-pentanedione-2-carboxylate (4g). Yellowish solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.32 (t, J = 7.2 Hz, 3H), 3.39 (m, 1H), 3.74 (m, 1H), 4.34 (q, J = 7.2 Hz, 2H), 4.81 (m, 1H), 7.14–7.69 (m, 9H), 7.90 (m, 2H), 8.15 (m, 1H), 8.38 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.6, 13.9, 39.2, 39.3, 39.8, 45.2, 45.5, 63.1, 63.6, 123.2, 123.7, 127.7, 128.0, 128.4, 128.6, 128.6, 129.5, 129.8, 129.9, 129.9, 131.0, 131.1, 133.2, 133.3, 136.4, 137.0, 149.6, 171.6, 172.5, 196.1; ^{19}F NMR ($CFCl_3$, 300 MHz) δ 169.0, 169.1; MS (ACPI) m/z: 464.2 (M^+ + 1).

Ethyl 1-phenyl-2-fluoro-3,5-di(4′-methoxyphenyl)-1,5-pentanedione-2-carboxylate (4h). White solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.26 (t, J = 7.2 Hz, 3H), 3.31 (m, 1H), 3.63 (m, 1H), 3.68 (s, 3H), 3.86 (s, 3H), 4.28 (q, J = 7.2 Hz, 2H), 4.68 (m, 1H), 6.67–6.91 (m, 4H), 7.27 (m, 4H), 7.47 (m, 2H), 7.71 (m, 1H), 7.90 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.8, 13.9, 39.2, 39.7, 44.5, 44.8, 55.0, 55.4, 62.6, 63.1, 113.5, 113.6, 113.7, 128.2, 128.6, 129.1, 129.2, 129.6, 130.0, 130.0, 130.4, 130.6, 130.9, 131.0, 134.1, 158.6, 163.5, 195.1, 195.2, 199.5, 200.3; ^{19}F NMR ($CFCl_3$, 300 MHz) δ 167.6, 167.7; MS (ACPI) m/z: 479.2 (M^+ + 1).

Ethyl 1-phenyl-2-fluoro-3-phenyl-5-styryl-1,5-pentanedione-2-carboxylate (4i). White solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.29 (t, J = 7.2 Hz, 3H), 3.06 (m, 1H), 3.35 (m, 1H), 4.32 (q, J = 7.2 Hz, 2H), 4.70 (m, 1H), 6.65 (d, J = 16.2 Hz, 1H), 7.10–7.53 (m, 14H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.7, 13.9, 41.6, 45.0, 45.3, 63.2, 125.8, 127.4, 127.8, 128.2, 128.3, 128.3, 128.6, 128.9, 129.1, 129.2, 129.5, 129.8, 129.9, 130.0, 130.0, 130.5, 130.6, 133.3, 134.2, 137.5, 142.9, 143.1, 196.4, 199.5, 200.2; ^{19}F NMR ($CFCl_3$, 300 MHz) δ 168.0, 168.1; MS (ACPI) m/z: 445.2 (M^+ + 1).

Typical procedure for one-pot fluorination and Robinson annulation

The β-ketoester **2d** (116 mg, 1 mmol) was added to a solution of Selectfluor™ (354 mg, 1 mmol) in CH_3CN (2 mL). After stirring at 90 °C for 40 min on a Biotage Initiator microwave instrument, the chalcone **3a** (208 mg, 1 mmol) and Cs_2CO_3 (100 mol%, 326 mg) were added and the mixture was then stirred at 90 °C for 30 min. EtOAc (10 mL) and H_2O (20 mL) were added. The organic layer was washed with aqueous HCl (2 M, 10 mL) and H_2O (10 mL), and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by flash column chromatography (6 : 1 hexane–EtOAc) to give fluorinated cyclohexenone compound **5a** (288 mg, 89%).

Methyl 2-ene-cyclohexanone-3,5-diphenyl-6-fluoro-6-carboxylate (5a). White liquid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.18 (m, J = 12.0 Hz, 2H), 3.67 (s, 3H), 3.84 (m, J = 12.0 Hz, 1H), 4.78 (m, 1H), 6.38 (s, 1H), 7.25–7.42 (m, 7H), 7.48–7.64 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 32.5, 32.6, 48.7, 48.9, 52.9, 122.4, 123.3, 126.2, 126.3, 127.4, 127.8, 128.3, 128.4, 128.7, 128.9, 130.7, 130.9, 136.1, 137.2, 161.3, 191.2; ^{19}F NMR ($CFCl_3$, 300 MHz) δ 166.2, 166.3; MS (ACPI) m/z: 325.1 (M^+ + 1).

Methyl 2-ene-cyclohexanone-3-(4′-methoxyphenyl)-5-phenyl-6-fluoro-6-carboxylate (5b). White liquid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.15 (m, 1H), 3.68 (s, 3H), 3.79 (m, 2H), 3.87 (s, 3H), 6.62 (s, 1H), 6.97 (m, 2H), 7.37 (m, 5H), 7.64 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 32.5, 32.6, 48.9, 49.1, 53.0, 55.6, 114.5, 121.6, 127.7, 128.0, 128.1, 128,3, 128.6, 128.9, 129.2, 129.4, 136.4, 160.8, 162.2, 192.0, 199.7, 200.9; ^{19}F NMR ($CFCl_3$, 300 MHz) δ 166.1, 166.2; MS (ACPI) m/z: 355.2 (M^+ + 1).

Methyl 2-ene-cyclohexanone-3-styryl-5-phenyl-6-fluoro-6-carboxylate (5c). White solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.05 (m, 2H), 3.62 (s, 3H), 3.71 (m, 1H), 6.21 (s, 1H), 6.92–7.12 (m, 2H), 7.37–7.53 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.6, 28.8, 47.0, 47.3, 53.0, 122.7, 126.5, 126.6, 128.3, 128.5, 128.9, 128.9, 129,1, 129.2, 129.2, 131.1, 131.2, 136.9, 137.6, 161.4, 190.4, 190.7; ^{19}F NMR ($CFCl_3$, 300 MHz) δ 165.6, 165.7; MS (ACPI) m/z: 351.2 (M^+ + 1).

3,5-Diphenyl-6-fluoro-6-acetyl-2-ene-cyclohexanone (5d). White liquid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.03 (d, J = 2.7 Hz, 3H), 3.08 (dd, J = 4.8 Hz, J = 18 Hz, 1H), 3.37 (dd, J = 4.8 Hz, J = 18 Hz, 1H), 3.98 (m, 1H), 6.58 (s, 1H), 7.26–7.48 (m, 8H), 7.56–7.61 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.6, 28.8, 31.7, 31.8, 47.0, 47.3, 122.5, 122.7, 126.5, 126.6, 128.3, 128.5, 128.9, 129.0, 129.1, 129.2, 129.2, 131.1, 131.2, 136.9, 137.6, 161.4, 190.4, 190.7; ^{19}F NMR ($CFCl_3$, 300 MHz) δ 164.2, 172.2, 172.4; MS (ACPI) m/z: 309.1 (M^+ + 1).

3-(4′-Methoxyphenyl)-5-phenyl-6-fluoro-6-acetyl-2-ene-cyclohexanone (5e). White liquid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.02 (d, J = 5.7 Hz, 3H), 3.04 (dd, J = 4.8 Hz, J = 18 Hz, 1H), 3.34 (dd, J = 4.8 Hz, J = 18 Hz, 1H), 3.85 (m, 1H), 3.89 (s, 3H), 6.53 (s, 1H), 6.55–7.00 (m, 2H), 7.28–7.41 (m, 5H), 7.53–7.58 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.3, 28.6, 31.1, 32.0, 46.7, 47.0, 55.4, 113.7, 114.3, 114.3, 120.3, 120.5, 121.7, 128.0, 128.1, 128.3, 128.7, 128.9, 129.0, 129.0, 129.3, 130.3, 130.8, 136.8, 143.9, 160.4, 161.9, 162.0, 190.2, 190.4, 207.2; ^{19}F NMR ($CFCl_3$, 300 MHz) δ 164.0, 172.0, 172.1; MS (ACPI) m/z: 339.1 (M^+ + 1).

3-Styryl-5-phenyl-6-fluoro-6-acetyl-2-ene-cyclohexanone (5f). White solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.01 (d, J = 5.4 Hz, 3H), 3.10 (m, 1H), 3.93 (m, 1H), 3.89 (s, 3H), 6.22 (s, 1H), 6.93–7.12 (m, 2H), 7.33–7.53 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.3, 28.6, 28.6, 46.4, 46.6, 48.4, 48.6, 125.1, 125.2, 127.5, 128.0, 128.3, 128.4, 128.8, 129.0, 129.0, 129.0, 129.0, 129.7, 129.7, 135.4, 135.5, 136.9, 137.3, 137.4, 158.2, 199.5; ^{19}F NMR ($CFCl_3$, 300 MHz) δ 163.6, 171.4, 171.6; MS (ACPI) m/z: 335.1 (M^+ + 1).

Ethyl 2-ene-cyclohexanone-3,5-diphenyl-4-fluoro-4-carboxylate (5g). White solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.08 (t, J = 7.2 Hz, 3H), 2.80 (m, 1H), 3.52 (m, 1H), 4.08 (m, 3H), 6.52 (s, 1H), 7.24–7.55 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 14.1, 39.3, 39.4, 49.0, 49.3, 62.8, 117.6, 127.7, 127.9, 127.9, 128.3, 128.6, 128.7, 128.7, 128.9, 129.0, 129.5, 129.6, 130.4, 135.7, 197.0; ^{19}F NMR ($CFCl_3$, 300 MHz) δ 178.7, 178.8; MS (ACPI) m/z: 309.1 (M^+ + 1).

Ethyl 2-ene-cyclohexanone-3-phenyl-5-(4′-chlorophenyl)-4-fluoro-4-carboxylate (5h). Yellowish solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.08 (t, J = 7.2 Hz, 3H), 3.42–3.79 (m, 1H), 3.78 (m, 2H), 4.21 (m, 1H), 4.41 (m, 1H), 5.66 (m, 1H), 7.17–7.74 (m, 7H), 7.83–7.94 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 14.1, 37.4, 44.8, 51.1, 59.6, 59.6, 88.1, 88.9, 91.6, 106.7, 127.6, 128.0, 128.2, 128.8, 128.9, 128.9, 129.0, 129.4, 129.4, 131.2, 133.1, 134.1, 134.3, 141.1, 170.1; ^{19}F NMR ($CFCl_3$, 300 MHz) δ 178.7, 178.8; MS (ACPI) m/z: 372.1 (M^+).

3,5-Diphenyl-6-fluoro-2-ene-cyclohexanone (5i). Yellowish liquid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.18 (dd, J = 12.1 Hz, 1H), 3.25 (dd, J = 12.1 Hz, 1H), 3.61 (m, J = 12.1 Hz, 1H), 4.96–5.03 (dd, J = 2.7 Hz, J = 20.1 Hz, 1H), 6.51 (s, 1H), 7.18–7.47 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 31.7, 31.8, 45.5, 45.7, 90.6, 93.0, 123.1, 126.5, 127.9, 128.3, 128.4, 128.8, 129.0, 129.1, 130.9, 137.9, 138.7, 160.1, 193.5; ^{19}F NMR ($CFCl_3$, 300 MHz) δ 199.9, 200.2; MS (ACPI) m/z: 267.1 (M^+ + 1).

3-Styryl-5-phenyl-6-fluoro-2-ene-cyclohexanone (5j). Yellowish liquid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.90 (dd, J = 12.1 Hz, 1H), 3.13 (m, 1H), 3.55 (m, 1H), 5.12–5.33 (dd, J = 12.6 Hz, J = 48.3 Hz, 1H), 6.21 (s, 1H), 6.96 (m, 2H), 7.26–7.55 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 32.9, 33.0, 46.7, 46.9, 91.3, 93.9, 126.0, 127.0, 127.4, 127.5, 127.6, 127.8, 128.1, 128.5, 128.8, 128.9, 130.0, 129.6, 130.9, 135.4, 137.0, 139.0,

155.6, 193.8, 200.4; ^{19}F NMR ($CFCl_3$, 300 MHz) δ 196.6, 196.7; MS (ACPI) *m*/*z*: 293.2 ($M^+ + 1$).

3-(4′-Methoxyphenyl)-5-phenyl-6-fluoro-2-ene-cyclohexanone (5k). Yellowish liquid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.12 (dd, J = 4.8 Hz, J = 18 Hz, 1H), 3.31 (dd, J = 1.8 Hz, J = 6.9 Hz, 1H), 3.84 (s, 1H), 3.87 (s, 3H), 4.91–5.09 (dd, J = 2.7 Hz, J = 20.1 Hz, 1H), 6.88 (d, J = 8.7 Hz, 2H), 7.30 (m, 5H), 7.50 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 31.2, 32.3, 45.2, 45.5, 55.4, 90.4, 92.8, 114.3, 121.0, 127.6, 128.0, 128.2, 128.2, 128.8, 129.7, 130.9, 138.7, 159.3, 161.8, 171.9, 193.1, 199.5; ^{19}F NMR ($CFCl_3$, 300 MHz) δ 199.7, 200.0; MS (ACPI) *m*/*z*: 297.1 ($M^+ + 1$).

4. Conclusions

We have developed a green and efficient one-pot synthesis procedure for fluorination of 1,3-dicarbonyl compounds followed by Michael addition or Robinson annulation with α,β-unsaturated ketones for the synthesis of acyclic and cyclic α-fluoro-β-ketoesters and α-fluoro-1,3-diketones. The decarboxylation can also be included in the one-pot reaction process by using a stronger base and heating the reaction at a higher temperature. High efficiency is realized by the microwave reaction combined with atom economic one-pot synthesis.

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