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Isocyanide-based MCRs: Diastereoselective cascade synthesis of perfluoroalkylated pyrano[3,4-*c*]pyrrole derivatives

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ABSTRACT

The highly diastereoselective synthesis of perfluoroalkyl-containing pyrano[3,4-*c*]pyrroles has been accomplished *via* a cascade process involving Michael addition, Passerini-type reaction, Mumm rearrangement and an *oxo*-Diels–Alder reaction. This domino transformation of isocyanides, methyl perfluoroalk-2-ynoates and 3-aroyl (or heteroyl) acrylic acids proceeded smoothly at room temperature and led to the formation of the highly diastereoselective target compounds with high functional-group compatibility in good to excellent yields.

1. Introduction

As is well known, incorporation of fluorine atoms or perfluoroalkyl moieties into bioactive organic molecules normally makes the resultant compounds improve their pharmacokinetic properties such as bioavailability, metabolic stability, and hydrolytic stability, etc [1]. For this reason, the development of methods for the construction of organofluorine compounds is of great importance.

Pyrano[3,4-*c*]-pyrrole moiety is found to exist in many biologically important natural products and some pharmaceuticals [2]. Recently, pyrano[3,4-*c*]-pyrrole derivatives are also found to be promising in organocatalytic field [3].

However, though a series of articles have been published to report the preparation of pyrano[3,4-*c*]-pyrrole derivatives [4], to our best knowledge, there is no literature available on the synthesis of perfluoroalkylated pyrano[3,4-*c*]-pyrroles. Therefore, the development of the methods for the construction of such organofluorine compounds is highly desirable.

Isocyanide-based multicomponent reactions (MCRs) take advantage of the unique properties of the isocyanide functional group and have become a versatile tool for the synthesis of structurally diverse heterocycles accompanied by many benefits such as facile execution, high atom-efficiency, regio-, chemo-, and stereoselectivity, etc [5].

In addition, owing to their economical and stereocontrolled nature, intramolecular hetero-Diels–Alder (IMHDA) reactions have been widely used in organic synthesis [6], thus providing a means for the diastereoselective construction of pyranopyrroles.

As a part of our ongoing research in the development of novel isocyanide-based MCRs for the synthesis of valuable perfluoroalkylated heterocyclic systems [7], we herein report a new diastereoselective route for the synthesis of perfluoroalkylated pyrano[3,4-*c*]-pyrrole derivatives based on the tandem Michael addition, Passerini-type reaction, Mumm rearrangement and an *oxo*-Diels–Alder reaction.

2. Results and discussion

Utilizing the isocyanide-based MCRs involved dimethyl acetylenedicarboxylate (DMAD), Jiang's group has accomplished the synthesis of densely functionalized pyrano[3,4-*c*]pyrroles at 80 °C in MeCN for 6 h [4]. Inspired by their work, we conducted a model reaction using (*E*)-4-oxo-4-phenylbut-2-enoic acid **1a**, *tert*-butyl isocyanide **2a** and methyl 4,4,4-trifluorobut-2-ynoate **3a** as model substrates under Jiang's conditions. To our delight, the desired product **4a** was obtained as a major diastereoisomer with moderate yield (Table 1, entry 1). The X-ray diffraction analysis shows unambiguously that **4a** is an *exo* adduct from IMHDA and its configuration is similar with those of the compounds

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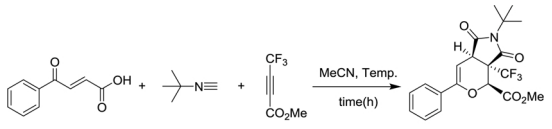
Table 1
Optimization of the reaction conditions[a].



1a 2a 3a 4a

Entry	Temperature [°C]	4Time [h]	Molar ratio [1a:2a:3a]	Yield [%][b]
1	80	6	1.0:1.2:1.2	64
2	r.t.	6	1.0:1.2:1.2	68
3	r.t.	6	1.0:1.1:1.1	65
4	**r.t.**	**12**	**1.0:1.1:1.1**	**82**[c]

[a] Reaction conditions: (*E*)-4-oxo-4-phenylbut-2-enoic acid **1a** (1.0 mmol), *tert*-butyl isocyanide **2a,** methyl 4,4,4-trifluorobut-2-ynoate **3a**, MeCN (5.0 mL) at the confined temperature for the specified time.
[b] Isolated yields.
[c] The *dr* value was confirmed to be 59:1 by ^{19}F NMR.

reported by Jiang and his co-workers (Fig. 1) [8]. Considering the volatility and low boiling point of **3a**, we lowered the reaction temperature to improve the yield but failed (Table 1, entry 2). Furthermore, when the reaction was conducted in a 1.0:1.1:1.1 instead of 1.0:1.2:1.2 M ratio, the yield did not be altered either. However, when prolonging the reaction time from 6 h to 12 h, there was an increase in the yield (Table 1, entry 4).

Having established the optimum reaction conditions (Table 1, entry 4), various R^1-substituted acrylic acids were first investigated to explore the applicability of the reaction. As shown in Table 2, moderate to excellent yields and high diastereoselectivities (**4a**–**4 r**, most cases >59:1 *dr*) were obtained with substrates containing various aryl or heteroaryl groups at the terminal position of acrylic acids. Generally, the electronic nature of substituents on the phenyl ring of **1** had a similar impact as reported by Jiang et al. on the yields of the desired products **4**. That is, electron-donating substituent on the phenyl ring of acrylic acid **1** afforded the desired products generally with lower yields compared to electron-withdrawing group at the same position (Table 2, entry 4 *vs* entries 5 and 6; entry 8 *vs* entry 9). For steric *ortho*-substituent, **4 j** was delivered in somewhat lower yield 81 % but still with high diastereoselectivity (>99:1 *dr*) (Table 2, entry 10).

In addition to the CF_3 group, other perfluoalky groups in the side chain of alkyne **3** were tested in the reaction (Table 2, entries 13–18). The substrates with CF_2H, C_2F_5, and *n*-C_3F_7 converted to the desired pyranopyrroles smoothly. Moreover, the increased steric hindrance of perfluoroalkyl group has only a little detrimental effect on the yields of the reaction and almost no adverse influence on diastereoselectivity (Table 2, entry 7 *vs* entries 13, 15 and 17).

The scope of the isocyanides was also examined. Different substituents R^2 on the nitrogen atom of **2** were proved to be compatible with the reaction, providing the products in moderate to excellent yields with high diastereoselectivity (32 – 98 %; >92:1 *dr*) (Table 2, entries 19–22). It should be mentioned that electron-withdrawing groups as 4-nitrophenyl somewhat retarded the annulation, and **2c** gives only a 32 % yield of **4 t** [11].

Encouraged by the above-mentioned results and to show the synthetic potential of the protocol, (*E*)-2-(1-*oxo*-1,3-dihydro-2*H*-inden-2-ylidene)acetic acid **1 m** and (*E*)-2-(1-*oxo*-3,4-dihydronaphthalen-2(1*H*)-ylidene)acetic acid **1n** were applied to the reaction and the corresponding adduct **4 w** and **4x** were obtained in good yield (71 %, 79 %) and (>99:1 *dr*) diastereoselectivity, respectively (Scheme 1).

Based on the experimental results and the previous reports [4,6,7,9], a mechanistic pathway is proposed (Scheme 2). Initially, Michael addition of **2** to perfluoroalkylated alkyne **3** gives zwitterion **I** which is immediately protonized by acrylic acid **1** to yield aminium **II** and carboxyl anion **III**. The intermediates **II** and **III** undergo Passerini-type reaction [10] to provide isoimide **IV**, followed by subsequent Mumm rearrangement [11] to deliver two conformers **V** and **V'** generated from single bond rotation (R_FCC(=O)-N). The final intramolecular *oxo*--Diels-Alder reaction affords *exo* adduct **4** as the major diastereoisomer; meanwhile, the unfavorable secondary orbital interaction and steric hindrance between R^1 group and CO_2Me group in conformer **V'** lead to the formation of *endo* isomer **4'** as the minor product [9].

3. Conclusions

We have developed a general and straightforward protocol for the synthesis of perfluoroalkylated pyrano[3,4-*c*]-pyrroles. This protocol, as a cascade process, involves domino Michael addition, Passerini-type reaction, Mumm rearrangement and an *oxo*-Diels–Alder reaction for various 3-aroyl (or heteroyl) acrylic acids, methyl perfluoroalk-2-ynoates and isocyanides. Advantages of this synthesis include mild reaction conditions, good to excellent yields, broad substrate scope and generally high diastereoselectivities. This protocol supplies an unprecedented avenue for an array of perfluoroalkylated pyranopyrroles which are interesting target compounds for screening biological activity.

4. Experimental

4.1. General information

Reagents and solvents were purchased from commercially sources

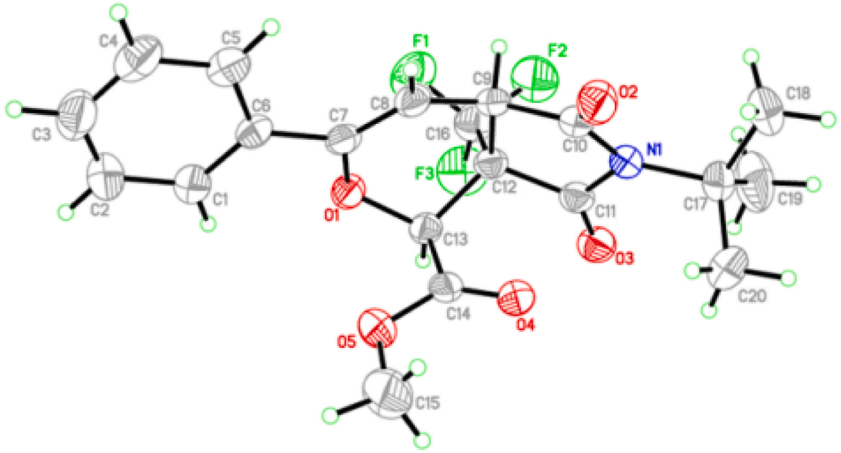


Fig. 1. X-ray crystal structure of compound **4a**.

and used without further purification. Methyl perfluoroalk-2-ynoates **3** [12], (*E*)-acrylic acids **1a-L** [13] and **1 m–n** [14] were prepared according to the known literatures. Melting points were recorded on a WRS-1 instrument and are uncorrected. ^{1}H, ^{19}F and ^{13}C NMR spectra were recorded on a Bruker DRX- 500 MHz spectrometer. All chemical shifts are reported in parts per million downfield (positive) of the standard: C_6F_6 for ^{19}F, TMS for ^{1}H and ^{13}C NMR spectra. IR spectra were obtained on an AVATAR370 FTIR spectrometer. LR-MS (lower resolution mass spectra) and HR-MS (high resolution mass spectra) were obtained on Agilent 6230, Thermo Fisher Scientific LTO FT Ultra and HP-5989 instruments, respectively. X-ray analysis was performed on a Bruker Smart Apex2 CCD spectrometer. Yields reported in this publication refer to isolated ones of compounds and their purity was determined by ^{1}H NMR.

4.2. General procedure for the synthesis of perfluoroalkylated pyrano [3,4-c]pyrrole derivatives 4

(*E*)-3-substituted acrylic acid **1** (1.0 mmol), isonitrile derivative **2** (1.1 mmol) and methyl perfluoroalk-2-ynoate **3** (1.1 mmol) were sequentially added to MeCN (5.0 mL). The resulted system was stirred for 12 h at room temperature. The solvent was evaporated under reduced pressure and the residue was purified by a short column chromatography on silica gel (eluent: petroleum ether:ethyl acetate = 20:1 to 5:1) to afford the purified product **4**.

4.2.1. Methyl 2-(tert-butyl)-1,3-dioxo-6-phenyl-3a-(trifluoromethyl)-1,2,3,3a,4,7a-hexahydropyrano [3,4-c]pyrrole-4-carboxylate (4a)

White solid; m.p.: 102.7-104.1 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.61 (s, 9 H), 3.49 (d, *J* =3.5 Hz, 1 H), 3.66 (s, 3 H), 5.42 (s, 1 H), 5.91 (d, *J* =3.5 Hz, 1 H), 7.36–7.38 (m, 3 H), 7.60–7.61 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 27.8, 38.5, 52.5 (q, $^{2}J_{C\text{-}F}$ =25.9 Hz, CF_3), 53.2, 59.6, 72.9, 94.2, 124.6 (q, $^{1}J_{C\text{-}F}$ =281.1 Hz, CF_3), 125.5, 128.5, 129.6, 133.2, 152.6, 166.9, 169.9, 174.0 ppm. ^{19}F NMR (470 MHz, $CDCl_3$) δ: -71.4 (s, CF_3) ppm. IR (KBr): *ν* 2984, 1741, 1709, 1653, 1451, 1342, 1274, 1186, 1171, 1088, 985 cm^{-1}. MS (EI) *m/z* (%): 411 $[M]^+$. HRMS (ESI) calcd. For $C_{20}H_{20}F_3NO_5$ $[(M+H)]^+$: 412.1373; found: 412.1371.

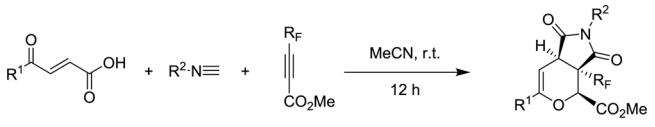
4.2.2. Methyl 2-(tert-butyl)-6-(4-methoxyphenyl)-1,3-dioxo-3a-(trifluoromethyl)-1,2,3,3a,4,7a-hexahydropyrano[3,4-c]pyrrole-4-carboxylate (4b)

Yellow solid; m.p.: 111.1–112.4 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.60 (s, 9 H), 3.46 (d, J =3.5 Hz, 1 H), 3.65 (s, 3 H), 3.82 (s, 3 H), 5.40 (s, 1 H), 5.76 (d, J =3.5 Hz, 1 H), 6.88–6.89 (m, 2 H), 7.53–7.55 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 27.8, 38.5, 52.6 (q, $^{2}J_{C\text{-}F}$ =25.7 Hz, CF_3), 53.2, 55.4, 59.5, 72.9, 92.3, 113.9, 124.6 (q, $^{1}J_{C\text{-}F}$ =281.2 Hz, CF_3), 125.8, 127.1, 152.6, 160.8, 167.0, 170.0, 174.3 ppm. ^{19}F NMR (470 MHz, $CDCl_3$) δ: -71.4 (s, CF_3) ppm. IR (KBr): *ν* 2958, 1749, 1714, 1654, 1463, 1345, 1273, 1171, 1077, 984 cm^{-1}. MS (EI) *m/z* (%): 441 $[M]^+$. HRMS (ESI) calcd. For $C_{21}H_{22}F_3NO_6$ $[(M+H)]^+$: 442.1478; found: 442.1473.

4.2.3. Methyl 2-(tert-butyl)-1,3-dioxo-6-(p-tolyl)-3a-(trifluoromethyl)-1,2,3,3a,4,7a-hexahydropyrano[3,4-c]pyrrole-4-carboxylate (4c)

Yellow solid; m.p.: 132.8-134.1 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.60 (s, 9 H), 2.36 (s, 3 H), 3.47 (d, *J* =3.5 Hz, 1 H), 3.65 (s, 3 H), 5.40 (s, 1 H), 5.84 (d, *J* =3.5 Hz, 1 H), 7.17 (d, *J* =8.0 Hz, 2 H), 7.49 (d, *J* =8.0 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.4, 27.8, 38.5, 52.6 (q, $^{2}J_{C\text{-}F}$ =25.9 Hz, CF_3), 53.2, 59.5, 72.9, 93.3, 124.6 (q, $^{1}J_{C\text{-}F}$ =281.1 Hz, CF_3), 125.5, 129.2, 129.4, 130.4, 139.8, 152.7, 167.0, 170.0, 174.2 ppm. ^{19}F NMR (470 MHz, $CDCl_3$) δ: -71.4 (s, CF_3) ppm. IR (KBr): *ν* 2976, 1740, 1711, 1654, 1457, 1341, 1276, 1184, 1165, 1086, 982 cm^{-1}. MS (EI) *m/z* (%): 425 $[M]^+$. HRMS (ESI) calcd. For $C_{21}H_{22}F_3NO_5$ $[(M+H)]^+$: 426.1529; found: 426.1525.

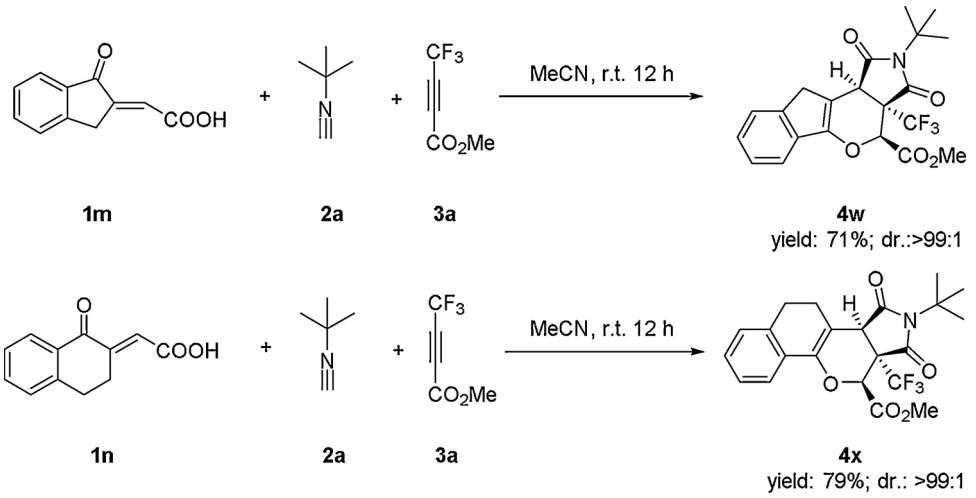
Table 2
Synthesis of perfluoroalkylated pyrano[3,4-*c*]-pyrroles 4[a].



1 2 3 4

Entry	R^1	R^2	R_F	Products	Yield [%][b]	*dr*[c]
1	C_6H_5 (**1a**)	*t*-Butyl (**2a**)	CF_3 (**3a**)	**4a**	83	59:1
2	4-$MeOC_6H_4$ (**1b**)	*t*-Butyl (**2a**)	CF_3 (**3a**)	**4b**	69	>99:1
3	4-MeC_6H_4 (**1c**)	*t*-Butyl (**2a**)	CF_3 (**3a**)	**4c**	87	>99:1
4	4-FC_6H_4 (**1d**)	*t*-Butyl (**2a**)	CF_3 (**3a**)	**4d**	95	>99:1
5	4-ClC_6H_4 (**1e**)	*t*-Butyl (**2a**)	CF_3 (**3a**)	**4e**	93	65:1
6	4-BrC_6H_4 (**1f**)	*t*-Butyl (**2a**)	CF_3 (**3a**)	**4f**	90	78:1
7	4-$NO_2C_6H_4$ (**1 g**)	*t*-Butyl (**2a**)	CF_3 (**3a**)	**4 g**	97	>99:1
8	3-MeC_6H_4 (**1 h**)	*t*-Butyl (**2a**)	CF_3 (**3a**)	**4 h**	85	85:1
9	3-$CF_3C_6H_4$ (**1i**)	*t*-Butyl (**2a**)	CF_3 (**3a**)	**4i**	94	>99:1
10	2-BrC_6H_4 (**1 j**)	*t*-Butyl (**2a**)	CF_3 (**3a**)	**4 j**	81	>99:1
11	2-Thienyl (**1k**)	*t*-Butyl (**2a**)	CF_3 (**3a**)	**4k**	90	75:1
12	2-Furyl (**1 L**)	*t*-Butyl (**2a**)	CF_3 (**3a**)	**4 L**	96	>99:1
13	4-$NO_2C_6H_4$ (**1 g**)	*t*-Butyl (**2a**)	CF_2H (**3b**)	**4 m**	92	>99:1
14	4-ClC_6H_4 (**1e**)	*t*-Butyl (**2a**)	CF_2H (**3b**)	**4n**	85	>99:1
15	4-$NO_2C_6H_4$ (**1 g**)	*t*-Butyl (**2a**)	C_2F_5 (**3c**)	**4o**	93	>99:1
16	C_6H_5 (**1a**)	*t*-Butyl (**2a**)	C_2F_5 (**3c**)	**4p**	64	>99:1
17	4-$NO_2C_6H_4$ (**1 g**)	*t*-Butyl (**2a**)	*n*-C_3F_7 (**3d**)	**4q**	89	85:1
18	C_6H_5 (**1a**)	*t*-Butyl (**2a**)	*n*-C_3F_7 (**3d**)	**4 r**	45	80:1
19	4-$NO_2C_6H_4$ (**1 g**)	Cyclohexyl (**2b**)	CF_3 (**3a**)	**4 s**	68	>99:1
20	4-$NO_2C_6H_4$ (**1 g**)	4-$NO_2C_6H_4$ (**2c**)	CF_3 (**3a**)	**4 t**	32	>99:1
21	4-$NO_2C_6H_4$ (**1 g**)	4-$MeOC_6H_4$(**2d**)	CF_3 (**3a**)	**4 u**	69	>99:1
22	4-$NO_2C_6H_4$ (**1 g**)	2,6-dimethylC_6H_4 (**2e**)	CF_3 (**3a**)	**4v**	98	92:1

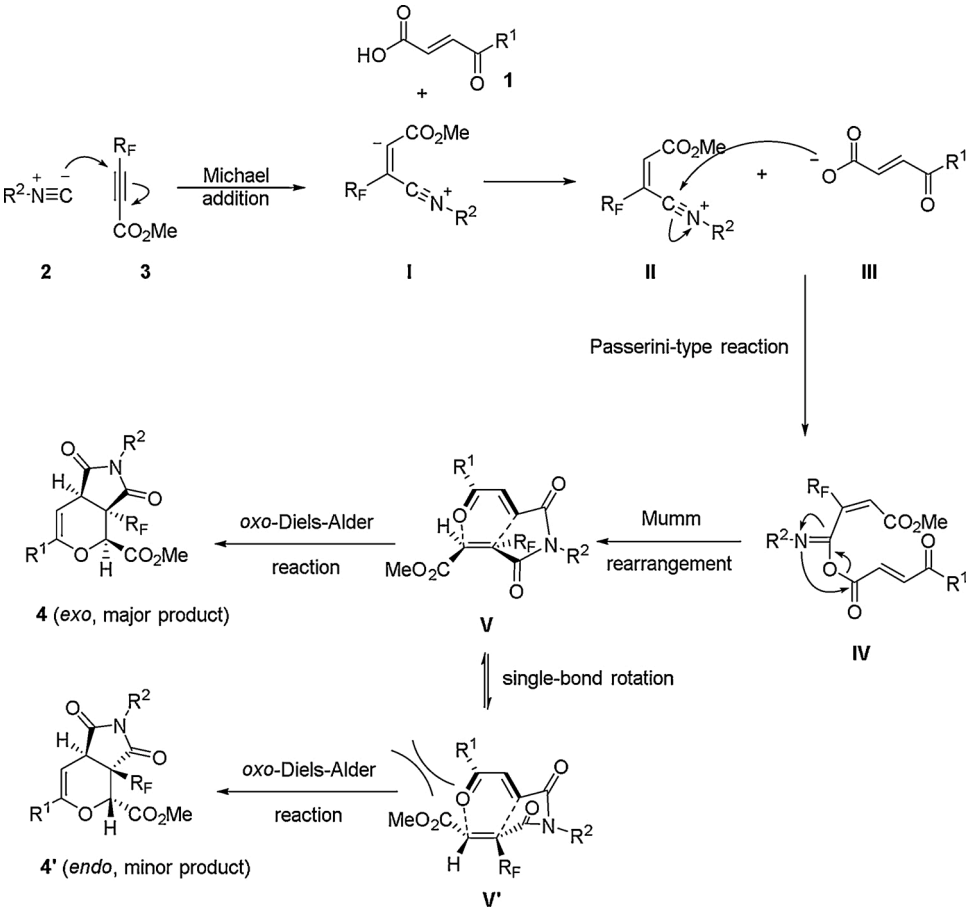
[a] Reaction conditions: (*E*)-4-oxobut-2-enoic acid derivative **1** (1.0 mmol), isocyanide derivative **2** (1.1 mmol), perfluoroalkylated alkyne **3** (1.1 mmol), MeCN (5.0 mL), room temperature, 12 h.
[b] Total isolated yield of two diastereoisomer.
[c] The *dr* value was confirmed by ^{19}F NMR.



Scheme 1. Substrate extension.

*4.2.4. Methyl 2-(tert-butyl)-6-(4-fluorophenyl)-1,3-dioxo-3a-(trifluoromethyl)-1,2,3,3a,4,7a-hexahydropyrano[3,4-c]pyrrole-4-carboxylate (**4d**)*

Yellow solid; m.p.: 89.9-91.2 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.60 (s, 9 H), 3.47 (d, J =3.5 Hz, 1 H), 3.66 (s, 3 H), 5.41 (s, 1 H), 5.84 (d, J =3.5 Hz, 1 H), 7.04–7.07 (m, 2 H), 7.57–7.60 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 27.8, 38.5, 52.5 (q, $^{2}J_{C\text{-}F}$ =25.8 Hz, CF_3), 53.3, 59.7, 72.9, 94.0, 115.6 (d, $^{2}J_{C\text{-}F}$ =21.8 Hz, ArF), 124.6 (q, $^{1}J_{C\text{-}F}$ =281.2 Hz, CF_3), 127.5, 127.6, 129.4, 151.8, 163.7 (d, $^{1}J_{C\text{-}F}$ =248.0 Hz, ArF), 166.8, 169.8, 174.0 ppm. ^{19}F NMR (470 MHz, $CDCl_3$) δ: -71.4 (s, CF_3), -111.3 (s, ArF) ppm. IR (KBr): ν 2952, 1754, 1703, 1654, 1512, 1459, 1339, 1275, 1208, 1178, 1103, 1080, 985 cm^{-1}. MS (EI) m/z (%): 429 $[M]^+$. HRMS (ESI) calcd. For $C_{20}H_{19}F_4NO_5$ $[(M+H)]^+$: 430.1278; found: 430.1274.



Scheme 2. Proposed mechanism for the synthesis of compound 4.

4.2.5. Methyl 2-(tert-butyl)-6-(4-chlorophenyl)-1,3-dioxo-3a-(trifluoromethyl)-1,2,3,3a,4,7a-hexahydropyrano[3,4-c]pyrrole-4-carboxylate (**4e**)

Yellow solid; m.p.: 121.7-123.0°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.60 (s, 9 H), 3.47 (d, J =3.5 Hz, 1 H), 3.65 (s, 3 H), 5.41 (s, 1 H), 5.90 (d, J =3.5 Hz, 1 H), 7.33–7.35 (m, 2 H), 7.53–7.55 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 27.8, 38.5, 52.5 (q, $^2J_{C\text{-}F}$ =25.8 Hz, CF_3), 53.3, 59.7, 72.9, 94.8, 124.6 (q, $^1J_{C\text{-}F}$ =281.2 Hz, CF_3), 126.8, 128.8, 131.6, 135.6, 151.6, 166.8, 169.7, 173.8 ppm. ^{19}F NMR (470 MHz, $CDCl_3$) δ: -71.4 (s, CF_3) ppm. IR (KBr): ν 2984, 1739 1710, 1654, 1496, 1344, 1274, 1183, 1167, 1092, 981 cm^{-1}. MS (EI) m/z (%): 445 $[M]^+$. HRMS (ESI) calcd. For $C_{20}H_{19}ClF_3NO_5$ $[(M+H)]^+$: 446.0983; found: 446.0984.

4.2.6. Methyl 6-(4-bromophenyl)-2-(tert-butyl)-1,3-dioxo-3a-(trifluoromethyl)-1,2,3,3a,4,7a-hexahydropyrano[3,4-c]pyrrole-4-carboxylate (**4f**)

White solid; m.p.: 140.7-142.1 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.60 (s, 9 H), 3.46 (d, J =4.0 Hz, 1 H), 3.65 (s, 3 H), 5.41 (s, 1 H), 5.91 (d, J =4.0 Hz, 1 H), 7.46–7.51 (m, 4 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 27.8, 38.5, 52.4 (q, $^2J_{C\text{-}F}$ =25.8 Hz, CF_3), 53.3, 59.7, 72.9, 94.9, 123.9, 124.6 (q, $^1J_{C\text{-}F}$ =281.2 Hz, CF_3), 127.0, 131.8, 132.1, 151.7, 166.8, 169.7, 173.8 ppm. ^{19}F NMR (470 MHz, $CDCl_3$) δ: -71.4 (s, CF_3) ppm. IR (KBr): ν 2983, 1737, 1709, 1654, 1493, 1343, 1273, 1185, 1167, 1087, 981 cm^{-1}. MS (EI) m/z (%): 489 $[M]^+$. HRMS (ESI) calcd. For $C_{20}H_{19}BrF_3NO_5$ $[(M+H)]^+$: 490.0478; found: 490.0465.

4.2.7. Methyl 2-(tert-butyl)-6-(4-nitrophenyl)-1,3-dioxo-3a-(trifluoromethyl)-1,2,3,3a,4,7a-hexahydropyrano[3,4-c]pyrrole-4-carboxylate (**4 g**)

Yellow solid; m.p.: 135.8-137.2 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.61 (s, 9 H), 3.53 (d, J =4.0 Hz, 1 H), 3.66 (s, 3 H), 5.47 (s, 1 H), 6.13 (d, J =4.0 Hz, 1 H), 7.77–7.79 (m, 2 H), 8.23–8.24 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 27.7, 38.6, 52.3 (q, $^2J_{C\text{-}F}$ =26.0 Hz, CF_3), 53.5, 59.9, 72.9, 98.3, 123.9, 124.5 (q, $^1J_{C\text{-}F}$ =281.2 Hz, CF_3), 126.1, 138.9, 148.4, 150.4, 166.5, 169.4, 173.3 ppm. ^{19}F NMR (470 MHz, $CDCl_3$) δ: -71.4 (s, CF_3) ppm. IR (KBr): ν 2979, 1748, 1710, 1653, 1525, 1351, 1271, 1191, 1167, 1078, 988 cm^{-1}. MS (EI) m/z (%): 456 $[M]^+$. HRMS (ESI) calcd. For $C_{20}H_{19}F_3N_2O_7$ $[(M+H)]^+$: 457.1223; found: 457.1212.

4.2.8. Methyl 2-(tert-butyl)-1,3-dioxo-6-(m-tolyl)-3a-(trifluoromethyl)-1,2,3,3a,4,7a-hexahydropyrano[3,4-c]pyrrole-4-carboxylate (**4 h**)

White solid; m.p.: 95.2-96.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.61 (s, 9 H), 2.37 (s, 3 H), 3.48 (d, J =4.0 Hz, 1 H), 3.66 (s, 3 H), 5.41 (s, 1 H), 5.88 (d, J =4.0 Hz, 1 H), 7.17–7.18 (m, 1 H), 7.24–7.27 (m, 1 H), 7.40–7.42 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.5, 27.8, 38.6, 52.5 (q, $^2J_{C\text{-}F}$ =25.8 Hz, CF_3), 53.2, 59.6, 72.8, 94.1, 122.7, 124.6 (q, $^1J_{C\text{-}F}$ =281.3 Hz, CF_3), 126.1, 128.5 130.4, 133.2, 138.2, 152.7, 166.9, 169.9, 174.1 ppm. ^{19}F NMR (470 MHz, $CDCl_3$) δ: -71.4 (s, CF_3) ppm. IR (KBr): ν 2983, 1745, 1709, 1653, 1437, 1356, 1276, 1181, 1106, 1086, 990 cm^{-1}. MS (EI) m/z (%): 425 $[M]^+$. HRMS (ESI) calcd. For $C_{21}H_{22}F_3NO_5$ $[(M+H)]^+$: 426.1529; found: 426.1526.

4.2.9. Methyl 2-(tert-butyl)-1,3-dioxo-3a-(trifluoromethyl)-6-(3-(trifluoromethyl)phenyl)-1,2,3,3a,4,7a-hexahydropyrano[3,4-c]pyrrole-4-carboxylate (**4i**)

Yellow solid; m.p.: 116.3-117.6 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.61 (s, 9 H), 3.51 (d, J =4.0 Hz, 1 H), 3.66 (s, 3 H), 5.46 (s, 1 H), 6.00 (d, J =4.0 Hz, 1 H), 7.49–7.52 (m, 1 H), 7.61–7.63 (m, 1 H), 7.77–7.79 (m, 1 H), 7.88 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 27.8, 38.5, 52.4 (q, $^2J_{C\text{-}F}$ =26.0 Hz, CF_3), 53.3, 59.8, 73.0, 96.1, 122.5, 124.0 (q, $^1J_{C\text{-}F}$ =270.7 Hz, $ArCF_3$), 124.6 (q, $^1J_{C\text{-}F}$ =281.2 Hz, CF_3), 126.2, 128.6, 129.1, 131.2 (q, $^2J_{C\text{-}F}$ =32.3 Hz, $ArCF_3$), 134.0, 151.3, 166.7, 169.6, 173.6 ppm. ^{19}F NMR (470 MHz, $CDCl_3$) δ: -62.9 (s, $ArCF_3$), -71.5 (s, CF_3) ppm. IR (KBr): ν 2988, 1752, 1716, 1655, 1439, 1351, 1261, 1187, 1169, 1088, 989 cm^{-1}. MS (EI) m/z (%): 479 $[M]^+$. HRMS (ESI) calcd. For $C_{21}H_{19}F_6NO_5$ $[(M+H)]^+$: 480.1246; found: 480.1247.

4.2.10. Methyl 6-(2-bromophenyl)-2-(tert-butyl)-1,3-dioxo-3a-(trifluoromethyl)-1,2,3,3a,4,7a-hexahydropyrano[3,4-c]pyrrole-4-carboxylate (**4 j**)

Yellow solid; m.p.: 74.1-75.4 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.60 (s, 9 H), 3.55 (d, J =4.0 Hz, 1 H), 3.76 (s, 3 H), 5.33 (s, 1 H), 5.75 (d, J =4.0 Hz, 1 H), 7.20–7.23 (m, 1 H), 7.30–7.33 (m, 1 H), 7.37–7.39 (m, 1 H),7.59–7.61 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 27.7, 38.4, 51.9 (q, $^2J_{C\text{-}F}$ =26.0 Hz, CF_3), 53.2, 59.6, 72.4, 99.3, 122.0, 124.4 (q, $^1J_{C\text{-}F}$ =281.3 Hz, CF_3), 127.4, 130.7, 130.8, 133.6, 134.9, 151.5, 166.6, 169.7, 173.5 ppm. ^{19}F NMR (470 MHz, $CDCl_3$) δ: -71.4 (s, CF_3) ppm. IR (KBr): ν 2975, 1748, 1714, 1439, 1335, 1274, 1185, 1166, 1078, 977 cm^{-1}. MS (EI) m/z (%): 489 $[M]^+$. HRMS (ESI) calcd. For $C_{20}H_{19}BrF_3NO_5$ $[(M+H)]^+$: 490.0478; found: 490.0475.

4.2.11. Methyl 2-(tert-butyl)-1,3-dioxo-6-(thiophen-2-yl)-3a-(trifluoromethyl)-1,2,3,3a,4,7a-hexahydropyrano[3,4-c]pyrrole-4-carboxylate (**4k**)

White solid; m.p.: 149.1-150.4 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.60 (s, 9 H), 3.46 (d, J =4.0 Hz, 1 H), 3.67 (s, 3 H), 5.38 (s, 1 H), 5.79 (d, J =4.0 Hz, 1 H), 7.01–7.03 (m, 1 H), 7.29–7.32 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 27.8, 38.3, 52.5 (q, $^2J_{C\text{-}F}$ =25.8 Hz, CF_3), 53.3, 59.7, 72.9, 93.4, 124.5 (q, $^1J_{C\text{-}F}$ =281.3 Hz, CF_3), 125.5, 127.0, 127.6, 136.9, 148.2, 166.8, 169.7, 173.9 ppm. ^{19}F NMR (470 MHz, $CDCl_3$) δ: -71.4 (s, CF_3) ppm. IR (KBr): ν 2984, 1743, 1709, 1652, 1435, 1313, 1266, 1185, 1162, 1073, 986 cm^{-1}. MS (EI) m/z (%): 417 $[M]^+$. HRMS (ESI) calcd. For $C_{18}H_{18}F_3NO_5S$ $[(M+H)]^+$: 418.0937; found: 418.0933.

4.2.12. Methyl 2-(tert-butyl)-6-(furan-2-yl)-1,3-dioxo-3a-(trifluoromethyl)-1,2,3,3a,4,7a-hexahydropyrano[3,4-c]pyrrole-4-carboxylate (4 L)

White solid; m.p.: 124.8-125.9 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.59 (s, 9 H), 3.49 (d, J =4.0 Hz, 1 H), 3.66 (s, 3 H), 5.33 (s, 1 H), 5.88 (d, J =4.0 Hz, 1 H), 6.41–6.42 (m, 1 H), 6.55–6.56 (m, 1 H), 7.40–7.41 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 27.8, 37.8, 52.4 (q, $^2J_{C\text{-}F}$ =25.9 Hz, CF_3), 53.3, 59.6, 72.5, 93.1, 108.9, 111.5, 124.5 (q, $^1J_{C\text{-}F}$ =281.2 Hz, CF_3), 143.6, 144.7, 147.7, 166.7, 169.8, 173.7 ppm. ^{19}F NMR (470 MHz, $CDCl_3$) δ: -71.5 (s, CF_3) ppm. IR (KBr): ν 2991, 1745, 1710, 1668, 1437, 1320, 1281, 1217, 1189, 1167, 1096, 879 cm^{-1}. MS (EI) m/z (%): 401 $[M]^+$. HRMS (ESI) calcd. For $C_{18}H_{18}F_3NO_6$ $[(M+H)]^+$: 402.1165; found: 402.1159.

4.2.13. Methyl 2-(tert-butyl)-3a-(difluoromethyl)-6-(4-nitrophenyl)-1,3-dioxo-1,2,3,3a,4,7a-hexahydropyrano[3,4-c]pyrrole-4-carboxylate (**4 m**)

Yellow solid; m.p.: 54.3-55.9 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.54 (s, 9 H), 3.75 (d, $J_{H\text{-}H}$ =5.0 Hz, 1 H), 3.91 (s, 3 H), 4.69 (s, 1 H), 6.04 (d, $J_{H\text{-}H}$ =5.0 Hz, 1 H), 6.51 (t, $J_{H\text{-}F}$ =55.5 Hz, 1 H), 7.77–7.79 (d, $J_{H\text{-}H}$ =8.0 Hz, 2 H), 8.21–8.23 (d, $J_{H\text{-}H}$ =8.0 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 28.0, 38.5, 53.3, 55.2 (t, $^2J_{C\text{-}F}$ =20.6 Hz, CF_2H), 60.0, 73.5, 99.3, 114.4 (t, $^1J_{C\text{-}F}$ =246.5 Hz, CF_2H), 123.9, 125.9, 138.6, 148.3, 151.6, 167.1, 172.6, 174.4 ppm. ^{19}F NMR (470 MHz, $CDCl_3$) δ: −129.3 to −127.6 (m, CF_2H) ppm. IR (KBr): ν 2959, 1745, 1710, 1524, 1439, 1348, 1268, 1190, 1129, 1067, 861 cm^{-1}. MS (EI) m/z (%): 438 $[M]^+$. HRMS (ESI) calcd. For $C_{20}H_{20}F_2N_2O_7$ $[(M+H)]^+$: 439.1318; found: 439.1347.

4.2.14. Methyl 2-(tert-butyl)-6-(4-chlorophenyl)-3a-(difluoromethyl)-1,3-dioxo-1,2,3,3a,4,7a-hexahydropyrano[3,4-c]pyrrole-4-carboxylate (**4n**)

Yellow solid; m.p.: 106.1-107.4 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.53 (s, 9 H), 3.70 (d, $J_{H\text{-}H}$ =5.0 Hz, 1 H), 3.91 (s, 3 H), 4.63 (s, 1 H), 5.80 (d, $J_{H\text{-}H}$ =4.5 Hz, 1 H), 6.50 (t, $J_{H\text{-}F}$ =55.5 Hz, 1 H), 7.32–7.34 (m, 2 H), 7.52–7.55 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 28.0, 38.5, 53.2, 55.5 (t, $^2J_{C\text{-}F}$ =20.6 Hz, CF_2H), 59.8, 73.5, 95.7, 114.5 (t, $^1J_{C\text{-}F}$ =246.3 Hz, CF_2H), 126.4, 128.8, 131.3, 135.6, 152.9, 167.4, 172.8, 174.9 ppm. ^{19}F NMR (470 MHz, $CDCl_3$) δ: −129.2 to −127.7 (m, CF_2H) ppm. IR (KBr): ν 2924, 1794, 1715, 1652, 1520, 1346, 1270, 1179, 1165, 1024, 855 cm^{-1}. MS (ESI) m/z (%): 428 $[M]^+$. HRMS (ESI) calcd.

For $C_{20}H_{20}ClF_2NO_5$ [(M+H)]$^+$: 428.1077; found: 428.1074.

4.2.15. Methyl 2-(tert-butyl)-6-(4-nitrophenyl)-1,3-dioxo-3a-(pentafluoroethyl)-1,2,3,3a,4,7a-hexahydropyrano[3,4-c]pyrrole-4-carboxylate (**4o**)

Yellow solid; m.p.: 125.5-127.1 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.59 (s, 9 H), 3.63 (d, J =4.0 Hz, 1 H), 3.65 (s, 3 H), 5.53 (s, 1 H), 6.16 (d, J =4.0 Hz, 1 H), 7.74–7.76 (d, J =9.0 Hz, 2 H), 8.22–8.24 (d, J =9.0 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 27.5, 38.3, 51.3 (t, $^2J_{C\text{-}F}$ =20.2 Hz, CF_2), 53.4, 59.7, 72.5, 98.9, 114.0 (tq, $^1J_{C\text{-}F}$ =262.4 Hz, $^2J_{C\text{-}F}$ =37.1 Hz, CF_2), 118.8 (qt, $^1J_{C\text{-}F}$ =286.6 Hz, $^2J_{C\text{-}F}$ =36.2 Hz, CF_3), 123.8, 125.9, 138.9, 148.3, 149.6, 166.5, 169.4, 173.0 ppm. ^{19}F NMR (470 MHz, $CDCl_3$) δ: -79.1 (s, CF_3), -117.6 – -115.8 (m, CF_2) ppm. IR (KBr): ν 2987, 1744, 1714, 1653, 1520, 1348, 1262, 1183, 1124, 1064, 948 cm^{-1}. MS (EI) m/z (%): 506 [M]$^+$. HRMS (ESI) calcd. For $C_{21}H_{19}F_5N_2O_7$ [(M+H)]$^+$: 507.1191; found: 507.1171.

4.2.16. Methyl 2-(tert-butyl)-1,3-dioxo-3a-(pentafluoroethyl)-6-phenyl-1,2,3,3a,4,7a-hexahydropyrano[3,4-c]pyrrole-4-carboxylate (**4p**)

Yellow solid; m.p.: 101.2-102.3 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.59 (s, 9 H), 3.59 (d, J =4.0 Hz, 1 H), 3.65 (s, 3 H), 5.50 (s, 1 H), 5.93 (d, J =4.0 Hz, 1 H), 7.35–7.38 (m, 3 H), 7.57–7.59 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 27.6, 38.3, 51.6 (t, $^2J_{C\text{-}F}$ =20.6 Hz, CF_2), 53.2, 59.5, 72.5, 94.8, 114.1 (tq, $^1J_{C\text{-}F}$ =262.4 Hz, $^2J_{C\text{-}F}$ =37.3 Hz, CF_2), 118.8 (qt, $^1J_{C\text{-}F}$ =287.0 Hz, $^2J_{C\text{-}F}$ =38.0 Hz, CF_3), 125.4, 128.5, 129.6, 133.2, 151.8, 166.8, 169.9, 173.8 ppm. ^{19}F NMR (470 MHz, $CDCl_3$) δ: -79.2 (s, CF_3), -116.7 – -115.9 (m, CF_2) ppm. IR (KBr): ν 2985, 1747, 1715, 1655, 1459, 1344, 1266, 1212, 1185, 1121, 1072, 945 cm^{-1}. MS (EI) m/z (%): 461 [M]$^+$. HRMS (ESI) calcd. For $C_{21}H_{20}F_5N_2O_5$ [(M+H)]$^+$: 462.1341; found: 462.1336.

4.2.17. Methyl 2-(tert-butyl)-6-(4-nitrophenyl)-1,3-dioxo-3a-(heptafluoropropyl)-1,2,3,3a,4,7a-hexahydropyrano[3,4-c]pyrrole-4-carboxylate (**4q**)

Yellow solid; m.p.: 125.6-127.1 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.59 (s, 9 H), 3.65–3.67 (m, 4 H), 5.57 (s, 1 H), 6.16 (d, J =3.5 Hz, 1 H), 7.74–7.77 (m, 2 H), 8.22–8.24 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 27.5, 38.5, 52.2 (t, $^2J_{C\text{-}F}$ =19.1 Hz, CF_2), 53.4, 59.8, 72.4, 98.8, 110.1 (tq, $^1J_{C\text{-}F}$ =266.9 Hz, $^2J_{C\text{-}F}$ =38.1 Hz, CF_2), 115.6 (m, CF_2), 117.5 (qt, $^1J_{C\text{-}F}$ =287.5 Hz, $^2J_{C\text{-}F}$ =33.3 Hz, CF_3), 123.8, 126.0, 138.9, 148.3, 149.7, 166.5, 169.4, 173.0 ppm. ^{19}F NMR (470 MHz, $CDCl_3$) δ: -80.6 – -80.3 (m, CF_3), -112.6 – -112.5 (m, CF_2), -122.5 – -122.4 (m, CF_2) ppm. IR (KBr): ν 2987, 1743, 1713, 1653, 1519, 1456, 1349, 1231, 1177, 1131, 1097, 901 cm^{-1}. MS (EI) m/z (%): 556 [M]$^+$. HRMS (ESI) calcd. For $C_{22}H_{19}F_7N_2O_7$ [(M+H)]$^+$: 557.1186; found: 557.1156.

4.2.18. Methyl 2-(tert-butyl)-1,3-dioxo-3a-(heptafluoropropyl)-6-phenyl-1,2,3,3a,4,7a-hexahydropyrano[3,4-c]pyrrole-4-carboxylate (**4r**)

Yellow solid; m.p.: 71.5-72.7 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.59 (s, 9 H), 3.62 (d, J =4.0 Hz, 1 H), 3.66 (s, 3 H), 5.53 (s, 1 H), 5.93 (d, J =4.0 Hz, 1 H), 7.35–7.38 (m, 3 H), 7.57–7.59 (m, 2 H), ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 27.6, 38.5, 52.5 (t, $^2J_{C\text{-}F}$ =20.6 Hz, CF_2), 53.2, 59.6, 72.5, 94.8, 110.2 (tq, $^1J_{C\text{-}F}$ =266.8 Hz, $^2J_{C\text{-}F}$ =37.9 Hz, CF_2), 116.0 (m, CF_2), 117.6 (qt, $^1J_{C\text{-}F}$ =287.7 Hz, $^2J_{C\text{-}F}$ =33.9 Hz, CF_3), 125.4, 128.5, 129.6, 133.2, 151.8, 166.8, 169.9, 173.8 ppm. ^{19}F NMR (470 MHz, $CDCl_3$) δ: -80.6 – -80.4 (m, CF_3), -112.7 – -112.6 (m, CF_2), -122.5 – -122.5 (m, CF_2) ppm. IR (KBr): ν 2979, 1746, 1710, 1654, 1451, 1334, 1227, 1191, 1136, 1050, 900 cm^{-1}. MS (EI) m/z (%): 511 [M]$^+$. HRMS (ESI) calcd. For $C_{22}H_{20}F_7NO_5$ [(M+H)]$^+$: 512.1308; found: 512.1304.

4.2.19. Methyl 2-cyclohexyl-6-(4-nitrophenyl)-1,3-dioxo-3a-(trifluoromethyl)-1,2,3,3a,4,7a-hexahydropyrano[3,4-c]pyrrole-4-carboxylate (**4s**)

Yellow solid; m.p.: 190.3-191.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.23–1.38 (m, 3 H), 1.66–1.73 (m, 3 H), 1.84–1.87 (m, 2 H), 2.04–2.15 (m, 2 H), 3.60 (d, J =4.0 Hz, 1 H), 3.65 (s, 3 H), 3.98–4.05 (m, 1 H), 5.49 (s, 1 H), 6.15 (d, J =4.0 Hz, 1 H), 7.79 (d, J =9.0 Hz, 2 H), 8.24 (d, J =9.0 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 25.1, 25.8, 28.1, 28.3, 38.5, 52.6 (q, $^2J_{C\text{-}F}$ =26.0 Hz, CF_3), 53.2, 53.4, 72.8, 98.1, 123.8, 124.4 (q, $^1J_{C\text{-}F}$ =281.3 Hz, CF_3), 126.1, 138.8, 148.4, 150.6, 166.4, 168.7, 172.4 ppm. ^{19}F NMR (470 MHz, $CDCl_3$) δ: -71.2 (s, CF_3) ppm. IR (KBr): ν 2942, 1742, 1715, 1654, 1529, 1437, 1350, 1211, 1190, 1083, 859 cm^{-1}. MS (ESI) m/z (%): 483 [M+H]$^+$. HRMS (ESI) calcd. For $C_{22}H_{21}F_3N_2O_7$ [(M+H)]$^+$: 483.1380; found: 483.1379.

4.2.20. Methyl 2,6-bis(4-nitrophenyl)-1,3-dioxo-3a-(trifluoromethyl)-1,2,3,3a,4,7a-hexahydropyrano[3,4-c]pyrrole-4-carboxylate (**4t**)

Yellow solid; m.p.: 193.8-195.1 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.70 (s, 3 H), 3.92 (d, J =4.0 Hz, 1 H), 5.65 (s, 1 H), 6.22 (d, J =4.0 Hz, 1 H), 7.64–7.67 (m, 2 H), 7.83–7.85 (m, 2 H), 8.27–8.29 (m, 2 H), 8.37–8.39 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 38.9, 53.3 (q, $^2J_{C\text{-}F}$ =26.5 Hz, CF_3), 54.0, 73.4, 97.1, 124.0, 124.2 (q, $^1J_{C\text{-}F}$ =281.7 Hz, CF_3), 124.7, 126.4, 127.4, 136.8, 138.4, 147.8, 148.7, 151.6, 167.1, 167.4, 170.9 ppm. ^{19}F NMR (470 MHz, $CDCl_3$) δ: -70.6 (s, CF_3) ppm. IR (KBr): ν 2926, 1741, 1733, 1654, 1524, 1348, 1277, 1213, 1197, 1171, 1078, 856 cm^{-1}. MS (ESI) m/z (%): 521 [M]$^+$. HRMS (ESI) calcd. For $C_{22}H_{14}F_3N_3O_9$ [(M+H)]$^+$: 522.0761; found: 522.0783.

4.2.21. Methyl 2-(4-methoxyphenyl)-6-(4-nitrophenyl)-1,3-dioxo-3a-(trifluoromethyl)-1,2,3,3a,4,7a-hexahydropyrano[3,4-c]pyrrole-4-carboxylate (**4u**)

Yellow solid; m.p.: 169.5-170.6 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.69 (s, 3 H), 3.84 (s, 3 H), 3.86 (d, J =4.0 Hz, 1 H), 5.61 (s, 1 H), 6.23 (d, J =4.0 Hz, 1 H), 7.00–7.02 (m, 2 H), 7.27–7.31 (m, 2 H), 7.82–7.84 (m, 2 H), 8.25–8.27 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 38.8, 53.1 (q, $^2J_{C\text{-}F}$ =26.2 Hz, CF_3), 53.7, 55.6, 73.1, 97.8, 114.8, 123.9, 124.4 (q, $^1J_{C\text{-}F}$ =281.5 Hz, CF_3), 126.2. 127.8, 138.7, 148.5, 151.1 160.2, 166.8, 168.2, 171.9 ppm. ^{19}F NMR (470 MHz, $CDCl_3$) δ: -70.8 (s, CF_3) ppm. IR (KBr): ν 2961, 1733, 1727, 1652, 1517, 1443, 1350, 1275, 1250, 1189, 1161, 1025, 975 cm^{-1}. MS (EI) m/z (%): 506 [M]$^+$. HRMS (ESI) calcd. For $C_{23}H_{17}F_3N_2O_8$ [(M+H)]$^+$: 507.0993; found: 507.0976.

4.2.22. Methyl 2-(2,6-dimethylphenyl)-6-(4-nitrophenyl)-1,3-dioxo-3a-(trifluoromethyl)-1,2,3,3a,4,7a-hexahydropyrano[3,4-c]pyrrole-4-carboxylate (**4v**)

Yellow solid; m.p.: 213.0-214.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.13 (s, 3 H), 2.16 (s, 3 H), 3.77 (s, 3 H), 3.97 (d, J =4.0 Hz, 1 H), 5.41 (s, 1 H), 6.27 (d, J =4.0 Hz, 1 H), 7.13–7.15 (m, 2 H), 7.24–7.27 (m, 1 H), 7.80–7.82 (m, 2 H), 8.25–8.27 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 17.9, 18.1, 40.1, 53.5, 54.9 (q, $^2J_{C\text{-}F}$ =25.8 Hz, CF_3), 72.9, 98.4, 124.0, 124.4 (q, $^1J_{C\text{-}F}$ =282.0 Hz, CF_3), 126.0. 128.8. 129.3, 130.1, 135.8, 137.1, 138.5, 148.5, 151.2, 166.1, 167.4, 171.2 ppm. ^{19}F NMR (470 MHz, $CDCl_3$) δ: -70.4 (s, CF_3) ppm. IR (KBr): ν 2956, 1770, 1727, 1653, 1514, 1440, 1341, 1248, 1220, 1206, 1116, 966 cm^{-1}. MS (ESI) m/z (%): 505 [M+H]$^+$. HRMS (ESI) calcd. For $C_{24}H_{19}F_3N_2O_7$ [(M+H)]$^+$: 505.1223; found: 505.1222.

4.2.23. Methyl 2-(tert-butyl)-1,3-dioxo-3a-(trifluoromethyl)-2,3,3a,4,6,10c-hexahydro-1H-indeno[1′,2′:5,6]pyrano[3,4-c]pyrrole-4-carboxylate (**4w**)

Yellow solid; m.p.: 155.4-157.2 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.63 (s, 9 H), 3.46 (d, J = 22 Hz, 1 H), 3.65 (s, 3 H), 3.76 (s, 1 H), 3.93 (d, J = 22 Hz, 1 H), 5.50 (s, 1 H), 7.28–7.31 (m, 1 H), 7.32–7.35 (m, 1 H), 7.42–7.43 (m, 1 H), 7.47–7.49 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 27.8, 36.0, 39.8, 51.9 (q, $^2J_{C\text{-}F}$ =26.0 Hz, CF_3), 53.4, 59.7, 73.4, 73.5, 108.6, 118.2, 124.3, 124.5 (q, $^1J_{C\text{-}F}$ =281.2 Hz, CF_3), 126.4, 126.6, 137.0, 141.9, 151.3, 166.9, 169.9, 173.5 ppm. ^{19}F NMR (470 MHz, $CDCl_3$) δ: -71.4 (s, CF_3) ppm. IR (KBr): ν 2964, 1741, 1709, 1654, 1493, 1364, 1273, 1189, 1124, 1065, 992 cm^{-1}. MS (ESI) m/z (%): 424 [M]$^+$. HRMS (ESI) calcd. For $C_{21}H_{20}F_3NO_5$ [(M+H)]$^+$: 424.1373; found: 424.1368.

*4.2.24. Methyl 1,3-dioxo-3a-(trifluoromethyl)-2-(trimethyl-l4-azanyl)-1,2,3,3a,4,6,7,11c-octahydrobenzo[f]cyclopenta[c]chromene-4-carboxylate (**4x**)*

Yellow solid; m.p.: 128.3-130.1°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.61 (s, 9 H), 2.47–2.53 (m, 1 H), 2.79–2.94 (m, 2 H), 3.06–3.13 (m, 1 H), 3.45 (s, 1 H), 3.66 (s, 3 H), 5.35 (s, 1 H), 7.13–7.15 (m, 1 H), 7.21–7.26 (m, 2 H), 7.51–7.52 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 24.8, 27.5, 27.7, 40.6, 52.2 (q, $^{2}J_{C\text{-}F}$ =25.9 Hz, CF_3), 53.1, 59.5, 71.9, 104.9, 121.9, 124.4 (q, $^{1}J_{C\text{-}F}$ =280.1 Hz, CF_3), 126.5, 127.3, 128.4, 129.5, 136.1, 145.6, 167.1, 169.6, 173.5 ppm. ^{19}F NMR (470 MHz, $CDCl_3$) δ: -71.4 (s, CF_3) ppm. IR (KBr): *ν* 2981, 1748, 1712, 1669, 1458, 1335, 1281, 1237, 1192, 1157, 1054, 981 cm^{-1}. MS (EI) *m/z* (%): 437 $[M]^+$. HRMS (ESI) calcd. For $C_{22}H_{22}F_3NO_5$ $[(M+H)]^+$: 438.1529; found: 438.1524.

Declaration of Competing Interest

The authors report no declarations of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jfluchem.2021.109723.

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