Expeditious Synthesis of Trifluoromethylated Heterocycles: Noncatalytic 1,3-Dipolar Cyclization of Azomethine Imines with (α-Trifluoromethyl)acrylates

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Abstract: A convenient, simple, and expeditious procedure for the preparation of novel trifluoromethylated bicyclic pyrazolidinone systems by noncatalytic 1,3-dipolar cyclization of azomethine imines with *tert*-butyl 2-(trifluoromethyl)prop-2-enoate is presented.

Key words: bicyclic compounds, fluorine, cycloadditions, heterocycles, imines, drugs

Heterocycles are an important group of structural units that are frequently encountered in biologically active natural products as well as in pharmaceuticals and agrochemicals.[1] Indeed, many heterocycles carrying a variety of substituents have been synthesized for a wide variety of medicinal applications during the last hundred years or so.[1] Partially fluorinated compounds, on the other hand, have only recently emerged as promising biologically active moieties for drug design.[2] These facts led us to explore efficient and simple routes for constructing fluorine-containing heterocycles to provide attractive surrogates for drug-like molecules.[3] Our group has been engaged in developing efficient and selective syntheses of fluorine-containing organic compounds.[4] Two principal strategies are generally considered when planning syntheses of fluorine-containing compounds: the direct introduction of fluorine atoms or fluorine-containing substituents into target molecules, or a building-block strategy involving the assembly of readily accessible fluorine-containing organic compounds as starting materials.[5] Although both approaches have their own particular advantages for syntheses of fluorinated molecules, the latter approach is especially attractive when the fluorinated building blocks are inexpensive and commercially available.[6] Among the group of easily accessible fluorine-containing building blocks, trifluoropyruvates have emerged as one of the most popular for the construction of fluorinated organic materials and they can provide valuable synthetic intermediates that can be converted into a variety of useful trifluoromethylated heterocycles.[7] On the other hand, despite their widespread use in polymer science, α-trifluoromethyl acrylates have not been actively studied for this purpose even though they are commercial available on a bulk scale.[8,9] We have therefore started a research program aimed at the effective use of α-trifluoromethyl acrylates for the synthesis of trifluoromethylated biologically interesting molecules.[10] *tert*-Butyl 2-(trifluoromethyl)prop-2-enoate (MAF-TBE®) is particularly attractive as a substrate because of its commercial availability on a bulk scale, its chemical stability resulting from the sterically demanding *tert*-butyl group, and the ease with which the *tert*-butyl ester moiety can be removed by acids. Here, we report a rapid synthesis of trifluoromethylated heterocycles by a noncatalytic 1,3-dipolar cyclization of azomethine imines with MAF-TBE.

The cycloaddition of 1,3-dipoles with olefins is one of the most powerful methods for the preparation of five-membered heterocycles.[11] In particular, the cycloaddition of azomethine imines with olefins[12] is of considerable interest because it permits the direct formation of biologically important bicyclic pyrazolidinone systems, potentially useful as antibiotics (Figure 1).[12f,j,13] Indeed, azomethine imines have been widely used as 1,3-dipoles in [3+2]-cycloaddition reactions; however, to the best of our knowledge, no example of the use of an α-trifluoromethyl acrylate as a cycloaddition partner has been reported. Furthermore, the reaction permits medicinally attractive trifluoromethylated bicyclic pyrazolidinone systems to be accessed in one step.

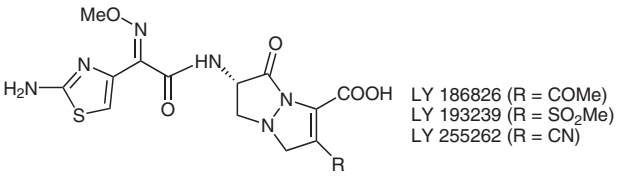

Figure 1 Examples of biologically active pyrazolidinone systems

We first examined the [3+2]-cycloaddition reaction of MAF-TBE with the azomethine imine **1a**, derived from benzaldehyde. We were surprised to find that the reaction proceeded without the help of a catalyst or additive when the reactants were stirred together in dichloromethane at room temperature for 20 hours to give the desired trifluoromethylated bicyclic pyrazolidinone **2a** in 96% yield as a 62:38 mixture of diastereoisomers (Table 1, entry 1). The solvent had little effect on the conversion (entries 2–4), although a longer reaction time was required in polar solvents such as *N*,*N*-dimethylformamide or methanol (entries 5 and 6). To understand the high reactivity involved in this transformation, we next attempted the reaction of **1a** with nonfluorinated methyl methacrylate under

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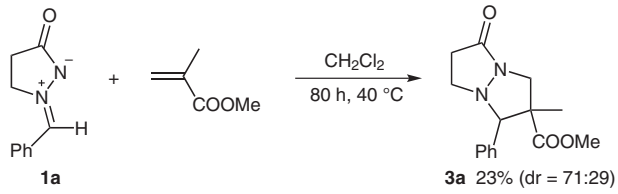
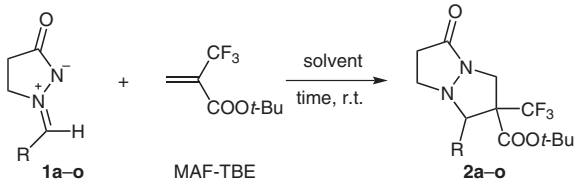
the same reaction conditions. In this case, only 23% of the corresponding product was obtained, even after 80 hours (Scheme 1).

We realized that the inherent properties of the fluorine atom, such as its powerful electron-withdrawing nature, are likely to play an important role in this noncatalytic cycloaddition reaction, so we examined the generality of this cycloaddition by using a series of azomethine imines. The reactions of the azomethine imines **1b–o** with MAF-TBE proceeded well to give the corresponding 1,3-dipolar cyclization products **2b–o** in high yields that were almost independent of the functional groups present, including alkyl, halo, methoxy, or sterically demanding naphthyl moieties, or of their positions on the aromatic ring (entries 7–17). We also obtained the bicyclic products **2m–n** in high yields from the corresponding aromatic analogues bearing hetaryl groups, although a slightly higher reaction temperature was required in these cases (entries 18 and 19). The cinnamyl-substituted azomethine imine **1o** is



Scheme 1 Reaction of **1a** with methyl methacrylate

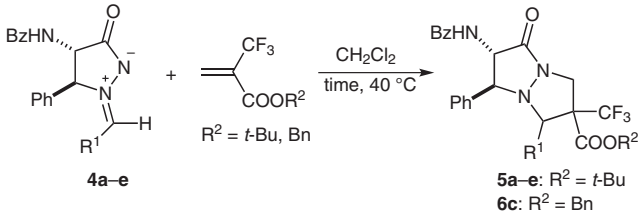
Table 1 Reactions of Azomethine Imines **1** with MAF-TBE



Entry[a]	Reactant	R	Solvent	Time (h)	Product	Yield (%)	dr[b]
1	**1a**	Ph	CH_2Cl_2	20	**2a**	96	62:38
2	**1a**	Ph	$CHCl_3$	24	**2a**	86	62:38
3	**1a**	Ph	THF	11	**2a**	88	60:40
4	**1a**	Ph	MeCN	43	**2a**	96	62:38
5	**1a**	Ph	DMF	192	**2a**	88	60:40
6	**1a**	Ph	MeOH	144	**2a**	82	66:34
7	**1b**	4-MeC_6H_4	CH_2Cl_2	21	**2b**	95	64:36
8	**1c**	4-*i*-PrC_6H_4	CH_2Cl_2	9	**2c**	79	63:37
9	**1d**	3,4-$Me_2C_6H_3$	CH_2Cl_2	5	**2d**	91	64:36
10	**1e**	4-$MeOC_6H_4$	CH_2Cl_2	9	**2e**	97	65:35
11	**1f**	2-$MeOC_6H_4$	CH_2Cl_2	70	**2f**	89	58:42
12	**1g**	3-$MeOC_6H_4$	CH_2Cl_2	10	**2g**	94	62:38
13[c]	**1h**	4-BrC_6H_4	CH_2Cl_2	14	**2h**	86	59:41
14	**1i**	4-ClC_6H_4	CH_2Cl_2	22	**2i**	87	61:39
15[c]	**1j**	3,5-$Br_2C_6H_3$	CH_2Cl_2	14	**2j**	84	52:48
16[d]	**1k**	1-naphthyl	CH_2Cl_2	5	**2k**	92	69:31
17[d]	**1l**	2-naphthyl	CH_2Cl_2	48	**2l**	85	63:37
18[c,d]	**1m**	2-furyl	CH_2Cl_2	48	**2m**	92	63:37
19[c,d]	**1n**	2-thienyl	CH_2Cl_2	90	**2n**	96	64:36
20	**1o**	(*E*)-PhCH=$CHCH_2$	CH_2Cl_2	25	**2o**	97	75:25

[a] Reaction conditions: **1** (0.1 mmol), MAF-TBE (0.2 mmol), solvent (1 mL), r.t. (unless otherwise stated).
[b] Determined by ^{19}F NMR analysis after purification.
[c] The reaction was carried out at 40 °C.
[d] CH_2Cl_2 (2.0 mL) was used.

Table 2 Reactions of Polysubstituted Azomethine Imines **4** with 2-(Trifluoromethyl)prop-2-enoate Esters



Entry[a]	Reactant[b]	R^1	R^2	Time (h)	Product	Yield (%)	dr[c]
1	**4a**	Ph	*t*-Bu	71	**5a**	94	70:20:8:2
2	**4b**	4-MeC_6H_4	*t*-Bu	58	**5b**	90	72:20:6:2
3	**4c**	4-$MeOC_6H_4$	*t*-Bu	26	**5c**	80	69:22:6:3
4	**4c**	4-$MeOC_6H_4$	Bn	28	**6c**	90	38:37:18:7
5	**4d**	4-BrC_6H_4	*t*-Bu	49	**5d**	38	67:19:10:4
6	**4e**	4-$O_2NC_6H_4$	*t*-Bu	65	**5e**	71	60:23:11:6

[a] Reaction conditions: **1** (0.1 mmol), MAF-TBE (0.2 mmol) CH_2Cl_2 (1 mL), r.t.
[b] Racemic **4** was used.
[c] Determined by ^{19}F NMR analysis after purification.

also suitable as a substrate for the noncatalytic cycloaddition, giving the cycloadduct **2o** in 97% yield (entry 20).

Encouraged by the success of the noncatalytic [3+2]-cycloaddition reaction of MAF-TBE with a series of azomethine imines, we next turned our attention to the 1,3-cycloaddition reactions of MAF-TBE with the polysubstituted pyrazolidinone azomethine imines **4a–e** to give polysubstituted 1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-1-ones, which could be useful as valuable scaffolds for the synthesis of conformationally constrained peptidomimetics.[13] Under reaction conditions similar to those used for the azomethine imine **1**, the polysubstituted benzoylamino pyrazolidinone azomethine imine **4** also gave the [3+2]-cycloaddition product **5** in a high yield regardless of the electronic nature of the substituents on the aromatic ring (Table 2, entries 1–6). When benzyl 2-(trifluoromethyl)prop-2-enoate was used instead of MAF-TBE in the reaction with azomethine imine **4c**, the corresponding benzyl ester **6c** was obtained in 90% yield (entry 4).

In summary, we have established a convenient, simple, expeditious, and inexpensive procedure for the preparation of novel trifluoromethylated bicyclic pyrazolidinone systems by the noncatalytic 1,3-dipolar cyclization of azomethine imines with MAF-TBE or related compounds. Further work is proceeding to develop asymmetric variants of the reaction, and efforts to incorporate this method into syntheses of peptidomimetics are underway.

All reactions were performed in oven-dried glassware under a positive pressure of N_2. Solvents were transferred by syringe and were introduced into the reaction vessels though rubber septa. All reactions were monitored by TLC on 0.25 mm Merck silica gel (60-F254). The TLC plates were visualized with UV light and 7% phosphomolybdic acid or aq $KMnO_4$ with heating. Column chromatography was carried out on a column packed with silica gel (60N spherical neutral, size 63–210 μm. The ^1H NMR (600 MHz), ^1H NMR (300 MHz), ^1H NMR (200 MHz), ^{19}F NMR (282 MHz), ^{19}F NMR (188 MHz), ^{13}C NMR (151 MHz), ^{13}C NMR (75.5 MHz), and ^{13}C NMR (50.2 MHz) spectra for solns in $CDCl_3$ were recorded on Buruker Avance 600, Varian Oxford 300, and Varian Mercury 200 spectrometers. Chemical shifts (δ) are expressed in ppm downfield from TMS or $CHCl_3$ as internal standards. Mass spectra were recorded on a Shimadzu GCMS-QP5050A or Shimadzu LCMS-2010EV spectrometers. IR spectra were recorded on a JASCO FT/IR-200 spectrophotometer.

tert-Butyl 5-Oxo-1-phenyl-2-(trifluoromethyl)tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-2-carboxylate (2a); Typical Procedure

MAF-TBE (35.8 μL, 0.20 mmol) was added slowly to a stirred soln of azomethine imine **1a** (17.4 mg, 0.10 mmol) in CH_2Cl_2 (1.0 mL) at r.t. under N_2, and the mixture was stirred for 20 h. The solvent was then removed under vacuum, and the crude product was purified by column chromatography [silica gel, hexane–EtOAc (6:4)] to give a white solid; yield: 35.7 mg (96%); dr = 62:38; mp 92.8–93.9 °C.

IR (KBr): 2985, 1726, 1457, 1370, 1335, 1301, 1261, 1171, 1137, 842, 743, 729, 700 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.47–7.32 (m, total 5 H, Ar-H), 4.48 (d, *J* = 12.8 Hz, 62/100 × 1 H, CH_2), 4.29 (d, *J* = 12.4 Hz, 38/100 × 1 H, CH_2), 4.21 (s, 62/100 × 1 H, Ar-C*H*), 4.08 (d, *J* = 12.4 Hz, 38/100 × 1 H, CH_2), 3.97 (s, 38/100 × 1 H, Ar-C*H*), 3.66–3.49 (m, total 1 H + 62/100 × 1 H, CH_2), 3.06–2.92 (m, total 1 H, CH_2), 2.85–2.61 (m, total 2 H, CH_2), 1.52 (s, 62/100 × 9 H, *t*-Bu), 1.02 (s, 38/100 × 9 H, *t*-Bu).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –66.1 (s, 62/100 × 3 F), –69.5 (s, 38/100 × 3 F).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 174.7, 174.2, 166.0, 163.4, 133.4, 132.1, 129.0, 128.8, 128.7, 128.6, 128.3, 128.1, 124.0 (q, *J* = 282 Hz), 119.7 (q, *J* = 280 Hz), 84.7, 83.8, 73.1, 72.1, 66.5 (q, *J* = 24.6 Hz), 65.9 (q, *J* = 24.3 Hz), 47.1, 46.4, 45.4, 45.2, 30.0, 29.9, 27.9, 27.3.

MS (EI): *m/z* = 370 $[M]^+$.

HRMS (EI): *m/z* calcd for $C_{18}H_{21}F_3N_2O_3$: 370.1504; found: 370.1519.

***tert*-Butyl 1-(4-Methylphenyl)-5-oxo-2-(trifluoromethyl)tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-2-carboxylate (2b)**
White solid; yield: 95%; dr = 64:36; mp 91.0–92.3 °C.

IR (KBr): 2978, 1715, 1516, 1456, 1370, 1259, 1182, 1076, 1054, 834, 762, 609 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.30 (m, total 2 H, Ar-H), 7.16–7.14 (m, total 2 H, Ar-H), 4.47 (d, *J* = 12.6 Hz, 64/100 × 1 H, CH_2), 4.27 (d, *J* = 12.3 Hz, 36/100 × 1 H, CH_2), 4.16 (s, 64/100 × 1 H, Ar-C*H*), 4.07 (d, *J* = 12.3 Hz, 36/100 × 1 H, CH_2), 3.94 (s, 36/100 × 1 H, Ar-C*H*), 3.63–3.50 (m, total 1 H + 64/100 × 1 H, CH_2), 3.02–2.92 (m, total 1 H, CH_2), 2.78–2.60 (m, total 2 H, CH_2), 2.35 (s, total 3 H, CH_3), 1.51 (s, 64/100 × 9 H, *t*-Bu), 1.03 (s, 36/100 × 9 H, *t*-Bu).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –66.3 (s, 64/100 × 3 F), –69.6 (s, 36/100 × 3 F).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 174.7, 174.3, 166.2, 163.7, 138.8, 138.5, 130.4, 129.0, 128.9, 128.7, 125.4 (q, *J* = 281 Hz), 124.2 (q, *J* = 283 Hz), 84.7, 83.8, 73.1, 72.0, 65.8 (q, *J* = 24.2 Hz), 47.0, 46.4, 45.4, 45.2, 30.1, 29.9, 27.8, 27.2, 21.3, 21.2 (one carbon atom resonance was not detected).

MS (EI): *m/z* = 384 $[M]^+$.

HRMS (EI): *m/z* calcd for $C_{19}H_{23}F_3N_2O_3$: 384.1661; found: 384.1674.

***tert*-Butyl 1-(4-Isopropylphenyl)-5-oxo-2-(trifluoromethyl)tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-2-carboxylate (2c)**
Pale yellow oil; yield: 79%; dr = 63:37.

IR (neat): 2963, 1731, 1461, 1370, 1304, 1257, 1170, 1080, 839, 610 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.34 (m, total 2 H, Ar-H), 7.21–7.18 (m, total 2 H, Ar-H), 4.46 (d, *J* = 12.3 Hz, 63/100 × 1 H, CH_2), 4.27 (d, *J* = 12.3 Hz, 37/100 × 1 H, CH_2), 4.18 (s, 63/100 × 1 H, Ar-C*H*N), 4.07 (d, *J* = 12.3 Hz, 37/100 × 1 H, CH_2), 3.96 (s, 37/100 × 1 H, Ar-C*H*), 3.64–3.51 (m, total 1 H + 63/100 × 1 H, CH_2), 3.05–2.86 [m, total 2 H, CH_2, $(CH_3)_2CH$], 2.78–2.61 (m, total 2 H, CH_2), 1.52 (s, 63/100 × 9 H, *t*-Bu), 1.25 (d, *J* = 10.2 Hz, 63/100 × 6 H, CH_3 × 2), 1.24 (d, *J* = 10.5 Hz, 37/100 × 6 H, CH_3 × 2), 1.01 (s, 37/100 × 9 H, *t*-Bu).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –66.3 (s, 63/100 × 3 F), –69.6 (s, 37/100 × 3 F).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 174.8, 174.4, 166.2, 163.6, 149.7, 149.3, 131.0, 129.8, 129.0, 128.7, 126.4, 126.2, 125.4 (q, *J* = 280 Hz), 124.1 (q, *J* = 283 Hz), 84.6, 83.7, 73.1, 72.0, 66.4 (q, *J* = 24.8 Hz), 65.7 (q, *J* = 24.2 Hz), 47.0, 46.3, 45.4, 45.2, 34.0, 33.9, 30.0, 29.9, 27.8, 27.2, 24.1, 24.0, 24.0, 23.9.

MS (EI): *m/z* = 412 $[M]^+$.

HRMS (EI): *m/z* calcd for $C_{21}H_{27}F_3N_2O_3$: 412.1974; found: 412.1971.

***tert*-Butyl 1-(3,4-Dimethylphenyl)-5-oxo-2-(trifluoromethyl)tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-2-carboxylate (2d)**
Pale yellow oil; yield: 91%; dr = 64:36.

IR (neat): 2979, 2937, 1731, 1714, 1504, 1456, 1395, 1370, 1352, 1301, 1217, 1144, 1083, 840 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.21–7.08 (m, total 3 H, Ar-H), 4.47 (d, *J* = 12.6 Hz, 64/100 × 1 H, CH_2), 4.26 (d, *J* = 12.6 Hz, 36/100 × 1 H, CH_2), 4.12–4.03 (m, total 1 H, Ar-C*H*, CH_2), 3.91 (s, 36/100 × 1 H, Ar-C*H*), 3.64–3.48 (m, total 1 H + 64/100 × 1 H, CH_2), 3.05–2.91 (m, total 1 H, CH_2), 2.84–2.57 (m, total 2 H, CH_2), 2.26 (s, total 6 H, CH_3 × 2), 1.52 (s, 64/100 × 9 H, *t*-Bu), 1.02 (s, 36/100 × 9 H, *t*-Bu).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –66.1 (s, 64/100 × 3 F), –69.5 (s, 36/100 × 3 F).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 174.8, 174.4, 166.4, 163.8, 137.5, 137.2, 136.6, 136.4, 130.9, 130.8, 130.1, 129.6, 129.6, 129.5, 126.8, 125.5 (q, *J* = 282 Hz), 126.3, 123.8 (q, *J* = 284 Hz), 84.6, 83.6, 73.4, 72.2, 66.5 (q, *J* = 24.1 Hz), 65.9 (q, *J* = 23.7 Hz), 46.9, 46.2, 45.4, 45.2, 30.0, 29.8, 27.7, 27.1, 19.7, 19.6, 19.5, 19.4.

MS (EI): *m/z* = 398 $[M]^+$.

HRMS (EI): *m/z* calcd for $C_{20}H_{25}F_3N_2O_3$: 398.1817; found: 398.1822.

***tert*-Butyl 1-(4-Methoxyphenyl)-5-oxo-2-(trifluoromethyl)tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-2-carboxylate (2e)**
Pale yellow oil; yield: 97%; dr = 65:35.

IR (neat): 2979, 2937, 1731, 1515, 1461, 1395, 1371, 1304, 1218, 1081, 838 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.41–7.34 (m, total 2 H, Ar-H), 6.89–6.86 (m, total 2 H, Ar-H), 4.47 (d, *J* = 12.6 Hz, 65/100 × 1 H, CH_2), 4.26 (d, *J* = 12.3 Hz, 35/100 × 1 H, CH_2), 4.14 (s, 65/100 × 1 H, Ar-C*H*), 4.06 (d, *J* = 12.9 Hz, 35/100 × 1 H, CH_2), 3.93 (s, 35/100 × 1 H, Ar-C*H*), 3.81 (s, 35/100 × 3 H,OCH_3), 3.80 (s, 65/100 × 3 H, OCH_3), 3.63–3.49 (m, total 1 H + 65/100 × 1 H, CH_2), 3.02–2.92 (m, total 1 H, CH_2), 2.78–2.60 (m, total 2 H, CH_2), 1.51 (s, 65/100 × 9 H, *t*-Bu), 1.06 (s, 35/100 × 9 H, *t*-Bu).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –66.3 (s, 65/100 × 3 F), –69.6 (s, 35/100 × 3 F).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 174.7, 174.3, 166.2, 163.7, 160.0, 159.7, 130.3, 130.0, 125.4 (q, *J* = 281 Hz), 125.3, 124.2 (q, *J* = 283 Hz), 123.9, 113.8, 113.6, 84.6, 83.7, 72.9, 71.8, 66.4 (q, *J* = 24.5 Hz), 65.6 (q, *J* = 23.9 Hz), 55.4, 55.2, 46.8, 46.4, 45.3, 45.1, 30.2, 29.8, 27.8, 27.3.

MS (EI): *m/z* = 400 $[M]^+$.

HRMS (EI): *m/z* calcd for $C_{19}H_{23}F_3N_2O_4$: 400.1610; found: 400.1611.

***tert*-Butyl 1-(2-Methoxyphenyl)-5-oxo-2-(trifluoromethyl)tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-2-carboxylate (2f)**
Colorless oil; yield: 89%; dr = 58:42.

IR (neat): 2978, 1731, 1602, 1590, 1494, 1463, 1369, 1305, 1254, 1189, 1078, 1049, 1027, 759 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.60–7.30 (m, total 2 H, Ar-H), 7.02–6.83 (m, total 2 H, Ar-H), 4.59–4.56 (m, total 1 H, CH_2, Ar-H), 4.34 (d, *J* = 12.6 Hz, 58/100 × 1 H, CH_2), 4.24 (s, 42/100 × 1 H, Ar-C*H*), 4.13 (d, 42/100 × 1 H, *J* = 12.4 Hz, CH_2), 3.81 (s, 42/100 × 3 H, OCH_3), 3.74 (s, 58/100 × 3 H, OCH_3), 3.69–3.40 (m, total 1 H + 58/100 × 1 H, CH_2), 3.15–2.93 (m, total 1 H, CH_2), 2.79–2.49 (m, total 2 H, CH_2), 1.55 (s, 58/100 × 9 H, *t*-Bu), 1.06 (s, 42/100 × 9 H, *t*-Bu).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –68.4 (s, 58/100 × 3 F), –69.3 (s, 42/100 × 3 F).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 177.3, 167.1, 167.1, 164.0, 158.5, 158.2, 129.9, 129.8, 129.5, 128.3, 124.3 (q, *J* = 283 Hz), 125.5 (q, *J* = 280 Hz), 122.6, 121.9, 120.7, 120.6, 110.4, 110.0, 83.7, 83.5, 67.8, 66.4 (q, *J* = 24.5 Hz), 64.1 (q, *J* = 23.4 Hz), 55.3, 55.1, 48.9, 48.9, 46.4, 45.4, 44.7, 43.9, 30.2, 29.1, 27.7, 27.2.

MS (EI): *m/z* = 400 $[M]^+$.

HRMS (EI): *m/z* calcd for $C_{19}H_{23}F_3N_2O_4$: 400.1610; found: 400.1613.

***tert*-Butyl 1-(3-Methoxyphenyl)-5-oxo-2-(trifluoromethyl)tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-2-carboxylate (2g)**
Colorless oil; yield: 94%; dr = 62:38.

IR (neat): 2979, 1731, 1602, 1586, 1491, 1457, 1370, 1301, 1155, 1080, 1051, 840, 698 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.30–7.21 (m, total 1 H, Ar-H), 7.07–7.02 (m, total 2 H, Ar-H), 6.90–6.86 (m, total 1 H, Ar-H), 4.46 (d, *J* = 12.6 Hz, 62/100 × 1 H, CH_2), 4.28 (d, *J* = 12.4 Hz, 38/100 × 1 H, CH_2), 4.19 (s, 62/100 × 1 H, Ar-C*H*), 4.09 (d, *J* = 12.6 Hz, 38/100 × 1 H, CH_2), 3.94 (s, 38/100 × 1 H, Ar-C*H*), 3.80 (s, total 3 H, OCH_3), 3.68–3.44 (m, total 1 H + 62/100 × 1 H, CH_2), 3.08–2.95 (m, total 1 H, CH_2), 2.85–2.52 (m, total 2 H, CH_2), 1.52 (s, 62/100 × 9 H, *t*-Bu), 1.05 (s, 38/100 × 9 H, *t*-Bu).

^1F NMR (188 MHz, $CDCl_3$): δ = –66.1 (s, 62/100 × 3 F), –69.5 (s, 38/100 × 3 F).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 175.0, 174.5, 166.3, 163.7, 159.8, 159.6, 135.2, 133.9, 129.5, 129.2, 125.5 (q, *J* = 282 Hz), 124.3 (q, *J* = 285 Hz), 121.7, 121.4, 121.4, 115.0, 114.5, 114.3, 84.7, 83.8, 73.1, 72.1, 66.5 (q, *J* = 24.1 Hz), 64.0 (q, *J* = 24.1 Hz), 55.3, 55.2, 47.0, 46.3, 45.4, 45.2, 29.8, 29.8, 27.7, 27.2.

MS (EI): *m/z* = 400 $[M]^+$.

HRMS (EI): *m/z* calcd for $C_{19}H_{23}F_3N_2O_4$: 400.1610; found: 400.1620.

***tert*-Butyl 1-(4-Bromophenyl)-5-oxo-2-(trifluoromethyl)tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-2-carboxylate (2h)**
White solid; yield: 86%; dr = 59:41; mp 107.8–109.1 °C.

IR (KBr): 2979, 1737, 1490, 1368, 1304, 1256, 1170, 1146, 1077, 1012, 838 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.52–7.32 (m, total 4 H, Ar-H), 4.4 (d, *J* = 12.8 Hz, 59/100 × 1 H, CH_2), 4.28 (d, *J* = 12.2 Hz, 41/100 × 1 H, CH_2), 4.16 (s, 59/100 × 1 H, Ar-C*H*), 4.05 (d, *J* = 12.4 Hz, 41/100 × 1 H, CH_2), 3.93 (s, 41/100 × 1 H, Ar-C*H*), 3.66–3.49 (m, total 1 H + 59/100 × 1 H, CH_2), 3.02–2.84 (m, total 1 H, CH_2), 2.78–2.61 (m, total 2 H, CH_2), 1.51 (s, 59/100 × 9 H, *t*-Bu), 1.06 (s, 41/100 × 9 H, *t*-Bu).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –66.2 (s, 59/100 × 3 F), –69.6 (s, 41/100 × 3 F).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 174.8, 174.4, 166.2, 163.5, 132.9, 131.7, 131.6, 131.5, 130.9, 130.7, 125.4 (q, *J* = 281 Hz), 124.2 (q, *J* = 284 Hz), 123.2, 122.9, 85.0, 84.2, 72.3, 71.5, 66.6 (q, *J* = 24.7 Hz), 66.0 (q, *J* = 24.4 Hz), 46.8, 46.4, 45.4, 45.1, 29.8, 29.6, 27.7, 27.2.

MS (EI): *m/z* = 448 $[M]^+$.

HRMS (EI): *m/z* calcd for $C_{18}H_{20}BrF_3N_2O_3$: 448.0609; found: 448.0613.

***tert*-Butyl 1-(4-Chlorophenyl)-5-oxo-2-(trifluoromethyl)tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-2-carboxylate (2i)**
White solid; yield: 87%; dr = 61:39; mp 108.3–110.0 °C.

IR (KBr): 2979, 1739, 1710, 1493, 1367, 1304, 1257, 1170, 1146, 1078, 838 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.48–7.25 (m, total 4 H, Ar-H), 4.47 (d, *J* = 12.6 Hz, 61/100 × 1 H, CH_2), 4.28 (d, *J* = 12.4 Hz, 39/100 × 1 H, CH_2), 4.18 (s, 61/100 × 1 H, Ar-C*H*), 4.06 (d, *J* = 12.4 Hz, 39/100 × 1 H, CH_2), 3.94 (s, 39/100 × 1 H, Ar-C*H*), 3.64–3.49 (m, total 1 H + 61/100 × 1 H, CH_2), 3.02–2.89 (m, total 1 H, CH_2), 2.85–2.61 (m, total 2 H, CH_2), 1.51 (s, 61/100 × 9 H, *t*-Bu), 1.06 (s, 39/100 × 9 H, *t*-Bu).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –66.1 (s, 61/100 × 3 F), –69.5 (s, 39/100 × 3 F).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 174.9, 174.5, 166.2, 163.6, 135.1, 134.7, 132.4, 131.1, 130.6, 130.4, 128.7, 128.6, 124.2 (q, *J* = 284 Hz), 124.1 (q, *J* = 288 Hz), 85.0, 84.2, 72.2, 71.5, 66.6 (q, *J* = 24.9 Hz), 66.0 (q, *J* = 24.4 Hz), 46.8, 46.4, 45.4, 45.1, 29.8, 29.6, 27.7, 27.2.

MS (EI): *m/z* = 404 $[M]^+$.

HRMS (EI): *m/z* calcd for $C_{18}H_{20}ClF_3N_2O_3$: 404.1115; found: 404.1128.

***tert*-Butyl 1-(3,5-Dibromophenyl)-5-oxo-2-(trifluoromethyl)tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-2-carboxylate (2j)**
Pale yellow oil: yield 84%; dr = 52:48.

IR (neat): 2980, 1731, 1714, 1585, 1557, 1426, 1371, 1349, 1299, 1256, 1173, 1084, 837, 742 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.67–7.50 (m, total 3 H, Ar-H), 4.50 (d, *J* = 12.8 Hz, 52/100 × 1 H, CH_2), 4.29 (d, *J* = 12.4 Hz, 48/100 × 1 H, CH_2), 3.69–3.53 (m, total 1 H, Ar-C*H*, CH_2) 3.88 (s, 48/100 × 1 H, Ar-C*H*), 3.69–3.53 (m, total 1 H + 52/100 × 1 H, CH_2), 3.03–2.89 (m, total 1 H, CH_2), 2.78–2.56 (m, total 2 H, CH_2), 1.53 (s, 52/100 × 9 H, *t*-Bu), 1.12 (s, 48/100 × 9 H, *t*-Bu).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –66.0 (s, 52/100 × 3 F), –69.6 (s, 48/100 × 3 F).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 174.7, 174.5, 165.9, 163.1, 138.2, 136.7, 134.5, 131.0, 125.3 (q, *J* = 281 Hz), 125.3, 124.0 (q, *J* = 286 Hz), 123.2, 122.8, 122.8, 85.5, 84.6, 71.4, 70.7, 66.7 (q, *J* = 25.0 Hz), 66.4 (q, *J* = 24.9 Hz), 46.7, 46.4, 45.6, 45.3, 29.7, 29.5, 27.7, 27.3.

MS (ESI): *m/z* = 526 $[M + H]^+$.

HRMS (EI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{19}Br_2F_3N_2O_3$: 525.9715; found: 525.9726.

***tert*-Butyl 1-(1-Naphthyl)-5-oxo-2-(trifluoromethyl)tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-2-carboxylate (2k)**
Pale yellow oil; yield: 92%; dr = 69:31.

IR (neat): 2979, 1732, 1596, 1458, 1371, 1301, 1260, 1188, 1077, 838, 786 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 8.06–7.40 (m, total 7 H, Ar-H), 5.06 (s, 69/100 × 1 H, Ar-C*H*), 4.86 (s, 31/100 × 1 H, Ar-C*H*), 4.51–3.45 (m, total 3 H, CH_2), 3.09–1.58 (m, total 3 H, CH_2), 1.58 (s, 69/100 × 9 H, *t*-Bu), 0.75 (s, 31/100 × 9 H, *t*-Bu).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –66.8 (s, 69/100 × 3 F), –68.4 (s, 31/100 × 3 F).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 176.8, 173.6, 167.6, 163.4, 133.7, 133.6, 132.6, 132.4, 130.6, 129.5, 129.3, 129.2, 128.9, 128.9, 127.7, 127.3, 126.6, 126.4, 125.8, 125.6, 125.5, 125.4, 125.3 (q, *J* = 281 Hz), 124.2 (q, *J* = 283 Hz), 122.5, 122.4, 85.0, 83.7, 69.7, 67.1 (q, *J* = 25.0 Hz), 65.4 (q, *J* = 24.4 Hz), 49.1, 46.1, 46.1, 45.0, 30.4, 29.2, 27.6, 26.9.

MS (EI): *m/z* = 420 $[M]^+$.

HRMS (EI): *m/z* calcd for $C_{22}H_{23}F_3N_2O_3$: 420.1661; found: 420.1677.

***tert*-Butyl 1-(2-Naphthyl)-5-oxo-2-(trifluoromethyl)tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-2-carboxylate (2l)**
Pale yellow oil; yield: 85%; dr = 63:37.

IR (neat): 2979, 1731, 1714, 1457, 1371, 1345, 1301, 1257, 1218, 1171, 1084, 838, 737 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.99–7.80 (m, total 4 H, Ar-H), 7.59–7.47 (m, total 3 H, Ar-H), 4.53 (d, *J* = 12.8 Hz, 63/100 × 1 H, CH_2), 4.37–4.30 (m, total 1 H, CH_2, Ar-C*H*), 4.18–4.09 (m, 37/

100 × 2 H, CH_2, Ar-H), 3.71–3.53 (m, total 1 H + 63/100 × 1 H, CH_2), 1.54 (s, 63/100 × 9 H, *t*-Bu), 0.83 (s, 37/100 × 9 H, *t*-Bu).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –66.0 (s, 63/100 × 3 F), –69.4 (s, 37/100 × 3 F).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 175.0, 174.5, 166.4, 163.7, 133.6, 133.5, 133.1, 133.1, 131.1, 129.9, 128.6, 128.1, 128.1, 128.1, 127.9, 127.7, 127.6, 126.7, 126.5, 126.3, 124.3 (q, *J* = 283 Hz), 84.8, 83.9, 73.3, 72.4, 66.8 (q, *J* = 26.3 Hz), 66.2 (q, *J* = 26.3 Hz), 47.0, 46.4, 45.5, 45.3, 29.9, 29.7, 27.8, 27.0 (one carbon atom resonance was not detected).

MS (EI): *m/z* = 420 $[M]^+$.

HRMS (EI): *m/z* calcd for $C_{22}H_{23}F_3N_2O_3$: 420.1661; found: 420.1656.

***tert*-Butyl 1-(2-Furyl)-5-oxo-2-(trifluoromethyl)tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-2-carboxylate (2m)**
White solid; yield: 92%; dr = 63:37; mp 93.3–95.2 °C.

IR (KBr): 2981, 1740, 1459, 1350, 1288, 1144, 1089, 1039, 768, 755, 719 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44–7.43 (m, total 1 H, Ar-H), 6.48–6.39 (m, total 2 H, Ar-H), 4.44 (d, *J* = 12.4 Hz, 63/100 × 1 H, CH_2), 4.35 (s, 63/100 × 1 H, Ar-C*H*), 4.20–4.15 (m, 37/100 × 3 H, Ar-C*H*, CH_2), 3.68 (d, *J* = 12.4 Hz, 63/100 × 1 H, CH_2), 3.54–3.44 (m, total 1 H, CH_2), 3.21–3.08 (m, total 1 H, CH_2), 2.80–2.57 (m, total 2 H, CH_2), 1.51 (s, 63/100 × 9 H, *t*-Bu), 1.24 (s, 37/100 × 9 H, *t*-Bu).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –67.9 (s, 63/100 × 3 F), –69.9 (s, 37/100 × 3 F).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 174.5, 174.3, 165.4, 163.2, 146.9, 145.8, 143.2, 124.9 (q, *J* = 282 Hz), 123.8 (q, *J* = 282 Hz), 110.9, 110.7, 110.6, 84.8, 84.1, 66.9, 65.5, 65.0 (q, *J* = 24.8 Hz), 46.4, 45.7, 45.2, 44.8, 30.2, 30.0, 27.7, 27.4 (one carbon atom resonance was not detected).

MS (EI): *m/z* = 360 $[M]^+$.

HRMS (EI): *m/z* calcd for $C_{16}H_{19}F_3N_2O_4$: 360.1297; found: 360.1311.

***tert*-Butyl 5-Oxo-1-(2-thienyl)-2-(trifluoromethyl)tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-2-carboxylate (2n)**
White solid; yield: 96%; dr = 64:36; mp 93.8–95.1 °C.

IR (KBr): 2979, 1728, 1459, 1372, 1348, 1297, 1251, 1219, 1147, 1085, 837, 786, 731, 709 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.35–7.00 (m, total 3 H, Ar-H), 4.51–4.45 (m, CH_2, 64/100 × 2 H, Ar-H), 4.31–4.25 (m, 36/100 × 2 H, CH_2, Ar-H), 4.14 (d, *J* = 12.4 Hz, 36/100 × 1 H, CH_2), 3.72–3.56 (m, total 1 H + 64/100 × H, CH_2), 3.17–2.61 (m, total 1 H, CH_2), 2.75–2.61 (m, total 2 H, CH_2), 1.52 (s, 64/100 × 9 H, *t*-Bu), 1.14 (s, 36/100 × 9 H, *t*-Bu).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –66.6 (s, 64/100 × 3 F), –69.7 (s, 36/100 × 3 F).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 174.5, 174.4, 166.0, 163.5, 136.1, 134.2, 128.1, 128.1, 127.1, 126.8, 126.5, 126.5, 125.3 (q, *J* = 281 Hz), 124.1 (q, *J* = 284 Hz), 85.0, 84.1, 69.2, 68.1, 66.5 (q, *J* = 24.9 Hz), 65.6 (q, *J* = 23.4 Hz), 46.5, 46.3, 45.7, 45.4, 29.8, 29.6, 27.7, 27.2.

MS (EI): *m/z* = 376 $[M]^+$.

HRMS (EI): *m/z* calcd for $C_{16}H_{19}F_3N_2O_3S$: 376.1068; found: 376.1065.

***tert*-Butyl 5-Oxo-1-styryl-2-(trifluoromethyl)tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-2-carboxylate (2o)**
Pale yellow solid; yield: 97%; dr = 75:25; mp 82.4–84.1 °C.

IR (KBr): 2983, 1740, 1709, 1456, 1368, 1263, 1231, 1173, 1084, 841, 744, 693 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.30 (m, total 5 H, Ar-H), 6.76 (d, *J* = 15.9, total 1 H, Ar-C*H*), 6.74 (d, *J* = 15.9, total 1 H, Ar-C*H*), 6.19–6.00 (m, total 1 H, ArCH=C*H*), 4.42 (d, *J* = 12.9 Hz, 75/100 × 1 H, CH_2), 4.22 (d, *J* = 12.3, 25/100 × 2 H, CH_2), 3.99 (d, *J* = 12.3, 25/100 × 2 H, CH_2), 3.68 (d, *J* = 8.1 Hz, 75/100 × 1 H, ArCH=CH*CH*), 3.63–3.50 (m, total 2 H, CH_2, ArCH=CHC*H*), 3.22–3.13 (m, total 1 H, CH_2), 2.80–2.58 (m, total 2 H, CH_2), 1.49 (s, 75/100 × 9 H, *t*-Bu), 1.37 (s, 25/100 × 9 H, *t*-Bu).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –66.1 (s, 75/100 × 3 F), –69.8 (s, 25/100 × 3 F).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 174.8, 174.6, 165.8, 164.3, 137.3, 136.4, 135.8, 135.4, 128.8, 128.7, 128.7, 128.5, 126.8, 126.6, 125.2 (q, *J* = 281 Hz), 124.5 (q, *J* = 284 Hz), 121.4, 120.7, 84.7, 84.5, 72.7, 70.9, 65.4 (q, *J* = 25.4 Hz), 64.9 (q, *J* = 24.4 Hz), 46.2, 44.8, 30.0, 29.7, 27.8, 27.7.

MS (EI): *m/z* = 396 $[M]^+$.

HRMS (EI): *m/z* calcd for $C_{20}H_{23}F_3N_2O_3$: 396.1661; found: 396.1678.

Methyl 2-Methyl-5-oxo-1-phenyltetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-2-carboxylate (3a)
Colorless oil; yield: 23%; dr = 71:29.

IR (neat): 3473, 2987, 2951, 2842, 1739, 1415, 1285, 1234, 1126, 1081, 986, 776, 750, 703 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.28 (m, total 5 H, Ar-H), 3.84 (s, 29/100 × 3 H, OCH_3), 3.82 (s, 71/100 × 3 H, OCH_3), 3.66–3.36 (m, total 2 H, CH_2, ArC*H*), 3.07–2.89 (m, total 1 H, CH_2), 2.82–2.55 (m, total 4 H, CH_2), 1.90 (s, 71/100 × 3 H, CH_3), 1.73 (s, 29/100 × 3 H, CH_3).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 172.4, 171.9, 164.6, 163.6, 136.6, 136.3, 128.7, 128.4, 128.3, 127.2, 127.1, 69.2, 69.2, 60.8, 60.7, 53.1, 53.0, 52.6, 51.9, 51.8, 51.1, 36.7, 36.1, 22.3, 22.1 (one carbon atom resonance was not detected).

MS (EI): *m/z* = 274 $[M]^+$.

HRMS (EI): *m/z* calcd for $C_{15}H_{18}N_2O_3$: 274.1317; found: 274.1313.

***tert*-Butyl 6-(Benzoylamino)-5-oxo-1,7-diphenyl-2-(trifluoromethyl)tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-2-carboxylate (5a)**
White solid; yield: 94%; dr = 70:20:8:2; mp 120.5–123.2 °C.

IR (KBr): 3381, 2977, 1739, 1699, 1666, 1538, 1458, 1371, 1305, 1262, 1193, 1087, 699 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): 7.71–6.92 (m, total 15 H, Ar-H), 5.23–5.14 (m, total 1 H, COC*H*), 4.78–4.52 (m, total 2 H, ArC*H*N, PhC*H*N), 4.19–3.95 (m, total 2 H, CH_2), 1.59 (s, 28/100 × 9 H, *t*-Bu), 1.58 (s, 28/100 × 9 H, *t*-Bu), 1.02 (s, 72/100 × 9 H, *t*-Bu), 0.98 (s, 72/100 × 9 H, *t*-Bu).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –64.8 (s, 20/100 × 3 F), –65.7 (s, 8/100 × 3 F), –69.3 (s, 2/100 × 3 F), –69.8 (s, 70/100 × 3 F).

MS (EI): *m/z* = 565 $[M]^+$.

HRMS (EI): *m/z* calcd for $C_{31}H_{30}F_3N_3O_4$: 565.2188; found: 565.2208.

The ^{13}C NMR spectrum of this compound is provided in the Supporting Information.

***tert*-Butyl 6-(Benzoylamino)-1-(4-methylphenyl)-5-oxo-7-phenyl-2-(trifluoromethyl)tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-2-carboxylate (5b)**

White solid; yield: 90%; dr = 72:20:6:2; mp 117.0–119.4 °C.

IR (KBr): 3322, 2981, 1740, 1716, 1653, 1541, 1457, 1302, 1251, 1153, 841, 697 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.70–7.59 (m, total 2 H, Ar-H), 7.48–7.14 (m, total 10 H, Ar-H), 6.94–6.65 (m, total 2 H, Ar-H), 5.18–5.11 (m, total 1 H, COC*H*), 4.91–4.30 (m, total 2 H, ArC*H*N, PhC*H*N), 4.10–3.78 (m, total 2 H, CH_2), 2.37 (s, total 3 H, CH_3), 2.32 (s, total 3 H, CH_3), 2.20 (s, total 3 H, CH_3), 1.80 (s, total 1 H, N*H*), 1.57 (s, 26/100 × 9 H, *t*-Bu), 1.54 (s, 26/100 × 9 H, *t*-Bu), 1.04 (s, 74/100 × 9 H, *t*-Bu), 1.00 (s, 74/100 × 9 H, *t*-Bu).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –65.3 (s, 20/100 × 3 F), –66.3 (s, 6/100 × 3 F), –69.9 (s, 2/100 × 3 F), –70.4 (s, 72/100 × 3 F).

MS (EI): *m/z* = 579 $[M]^+$.

HRMS (EI): *m/z* calcd for $C_{32}H_{32}F_3N_3O_4$: 579.2345; found: 579.2368.

The ^{13}C NMR spectrum of this compound is provided in the Supporting Information.

***tert*-Butyl 6-(Benzoylamino)-1-(4-methoxyphenyl)-5-oxo-7-phenyl-2-(trifluoromethyl)tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-2-carboxylate (5c)**

White solid; yield: 80%; dr = 69:22:6:3; mp 119.3–122.4 °C.

IR (KBr): 3322, 3064, 2979, 1739, 1714, 1669, 1515, 1457, 1302, 1253, 837, 697 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.73–7.60 (m, total 2 H, Ar-H), 7.43–7.17 (m, total 8 H, Ar-H), 6.97–6.57 (m, total 4 H, Ar-H), 5.16–5.09 (m, total 1 H, COC*H*), 4.86–4.52 (m, total 2 H, ArC*H*N, PhC*H*N), 4.12–3.93 (m, total 2 H, CH_2), 3.83 (s, total 3 H, MeO), 3.78 (s, total 3 H, MeO), 3.68 (s, total 1 H, N*H*), 1.81 (s, 28/100 × 9 H, *t*-Bu), 1.07 (s, 72/100 × 9 H, *t*-Bu), 1.03 (s, 72/100 × 9 H, *t*-Bu).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –64.9 (s, 22/100 × 3 F), –66.0 (s, 6/100 × 3 F), –69.5 (s, 3/100 × 3 F), –70.0 (s, 69/100 × 3 F).

MS (EI): *m/z* = 595 $[M]^+$.

HRMS (EI): *m/z* calcd for $C_{32}H_{32}F_3N_3O_5$: 595.2294; found: 595.2299.

The ^{13}C NMR spectrum of this compound is provided in the Supporting Information.

***tert*-Butyl 6-(Benzoylamino)-1-(4-bromophenyl)-5-oxo-7-phenyl-2-(trifluoromethyl)tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-2-carboxylate (5d)**

White solid; yield: 38%; dr = 67:19:10:4; mp 194.8–198.3 °C.

IR (KBr): 3382, 2979, 1737, 1706, 1665, 1540, 1457, 1305, 1251, 837, 697 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.69–7.63 (m, total 2 H, Ar-H), 7.46–7.11 (m, total 12 H, Ar-H), 5.16–5.10 (m, total 1 H, COCH), 4.71–4.44 (m, total 2 H, ArC*H*N, PhC*H*N), 4.24–4.09 (m, total 2 H, CH_2), 1.64 (s, 28/100 × 9 H, *t*-Bu), 1.59 (s, 28/100 × 9 H, *t*-Bu), 1.07 (s, 72/100 × 9 H, *t*-Bu), 1.02 (s, 72/100 × 9 H, *t*-Bu).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –65.3 (s, 19/100 × 3 F), –66.4 (s, 10/100 × 3 F), –69.9 (s, 4/100 × 3 F), –70.3 (s, 67/100 × 3 F).

MS (EI): *m/z* = 643 $[M]^+$.

HRMS (EI): *m/z* calcd for $C_{31}H_{29}BrF_3N_3O_4$: 643.1294; found: 643.1323.

The ^{13}C NMR spectrum of this compound is provided in the Supporting Information.

***tert*-Butyl 6-(Benzoylamino)-1-(4-nitrophenyl)-5-oxo-7-phenyl-2-(trifluoromethyl)tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-2-carboxylate (5e)**

Yellow solid; yield: 71%; dr = 60:23:11:6; mp 190.7–194.5 °C.

IR (KBr): 3447, 3065, 2981, 1735, 1716, 1524, 1349, 1301, 1251, 1151, 833, 697 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.38–7.74 (m, total 4 H, Ar-H), 7.45–7.06 (m, total 10 H, Ar-H), 5.31–4.98 (m, total 1 H, COC*H*), 4.87–4.47 (m, total 2 H, ArC*H*N, PhC*H*N), 4.27–3.83 (m, total 2 H, CH_2), 3.75 (s, total 1 H, N*H*), 3.36 (s, total 1 H, N*H*), 1.64 (s, 34/100 × 9 H, *t*-Bu), 1.59 (s, 34/100 × 9 H, *t*-Bu), 1.05 (s, 66/100 × 9 H, *t*-Bu), 0.99 (s, 66/100 × 9 H, *t*-Bu).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –64.8 (s, 23/100 × 3 F), –66.0 (s, 11/100 × 3 F), –69.4 (s, 6/100 × 3 F), –70.1 (s, 60/100 × 3 F).

MS (EI): *m/z* = 610 $[M]^+$.

HRMS (EI): *m/z* calcd for $C_{31}H_{29}F_3N_4O_6$: 610.2039; found: 610.2028.

The ^{13}C NMR spectrum of this compound is provided in the Supporting Information.

Benzyl 6-(Benzoylamino)-1-(4-methoxyphenyl)-5-oxo-7-phenyl-2-(trifluoromethyl)tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-2-carboxylate (6c)

White solid; yield: 90%; dr = 37:7:38:18; mp 89.8–93.8 °C.

IR (KBr): 3324, 3033, 2958, 1745, 1654, 1515, 1456, 1253, 1179, 1073, 1031, 749, 697 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.86–6.44 (m, total 19 H, Ar-H), 5.46–5.31 (m, total 1 H, COC*H*), 5.28–3.99 (m, total 6 H, ArC*H*N, PhC*H*N, NCH_2, PhCH_2), 3.83 (s, total 3 H, OCH_3), 3.75 (s, total 3 H, OCH_3), 3.67 (s, total 3 H, OCH_3), 3.67 (s, total 3 H, OCH_3).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –65.2 (s, 7/100 × 3 F), –66.3 (s, 38/100 × 3 F), –69.4 (s, 18/100 × 3 F), –70.0 (s, 37/100 × 3 F).

MS (EI): *m/z* = 629 $[M]^+$.

HRMS (EI): *m/z* calcd for $C_{35}H_{30}F_3N_3O_5$: 629.2138; found: 629.2141.

The ^{13}C NMR spectrum of this compound is provided in the Supporting Information.

Supporting Information for this article (^{13}C NMR spectra of compounds **5a–e** and **6c**) is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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