Baylis–Hillman Reactions of 2-(Trifluoroacetyl)-1,3-azoles

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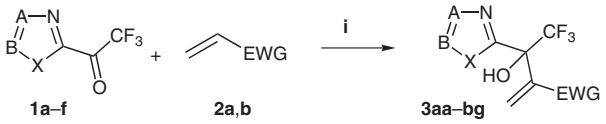
Abstract: 2-(Trifluoroacetyl)-1,3-azoles readily react with methyl acrylate and acrylonitrile under Baylis–Hillman reaction conditions to afford heterocyclic trifluoromethyl-containing allylic alcohols in 36–97% yields. The thus obtained Baylis–Hillman adducts readily undergo Michael addition reactions with various nucleophiles.

Key words: Baylis–Hillman reaction, 1,3-azoles, Michael additions, trifluoromethyl substituted, allylic alcohols



EWG = **a:** CN, **b:** CO_2Me
A, B, X for compounds shown, see Table 1

Scheme 1 *Reagents and conditions*: (i) DABCO (0.05 equiv), THF or neat, r.t., 30 min to 7 d.

The Baylis–Hillman reaction provides an efficient methodology for the formation of C–C bonds[1] through the base-catalyzed α-oxyalkylation of activated alkenes with, aldehydes, *N*-sulfonylimines, and activated ketones (e.g., hexafluoroacetone and trifluoropyruvates,[2a] isatins and ninhydrin[2b]). Less electrophilic ketones react under harsher conditions to give the target compounds in moderate or low yields.[3]

Recently we synthesized a set of highly electrophilic 2-(trifluoroacetyl)-1,3-azoles[4] that are potential reagents for the Baylis–Hillman reaction leading to novel polyfunctionalized trifluoromethyl-containing allyl alcohols. Ketones **1a–f** reacted with acrylonitrile (**2a**) in tetrahydrofuran at room temperature in the presence of 1,4-diazabicyclo[2.2.2]octane to give products **3aa–af** in 55–74% yield (Scheme 1, Table 1). The reaction took 3–5 days and resulted in 85–90% conversion according to ^{19}F NMR spectral studies of the reaction mixtures.

The Baylis–Hillman reactions of methyl acrylate (**2b**) with ketones **1** gave target compounds **3ba–bg** in 36–46% yield after ten days of stirring in tetrahydrofuran. Several unidentified side products were detected by ^{1}H NMR spectroscopic studies of the reaction mixtures. In order to improve the selectivity, the Baylis–Hillman reactions were carried out at ambient temperature in a mixture of neat reagents. Such a simple modification of the synthetic procedure increased the yield of target compounds to 80–97% and decreased the reaction time to 1–12 hours (Table 1).

Table 1 Synthesis of the Baylis–Hillman Adducts

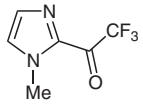
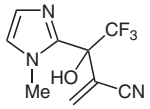
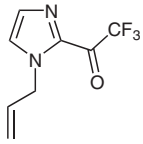
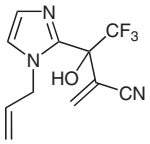
Entry	Ketone	Alkene	Conditions	Product	Yield[a] (%)
1	 **1a**	**2a**	THF, r.t., 5 d	 **3aa**	74
2	 **1b**	**2a**	THF, r.t., 5 d	 **3ab**	62

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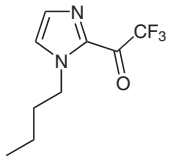
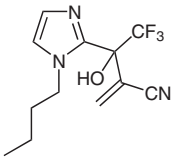
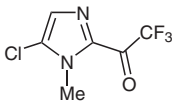
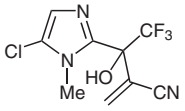
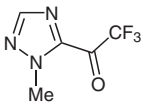
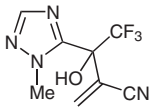
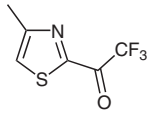
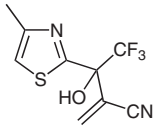
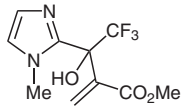
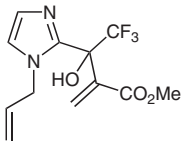
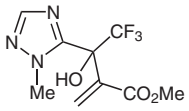
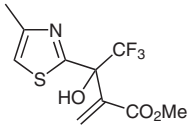
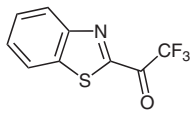
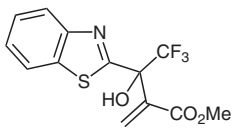
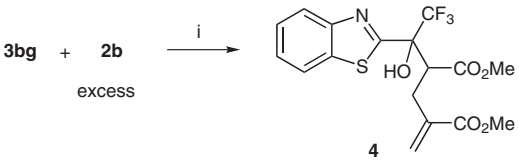
Table 1 Synthesis of the Baylis–Hillman Adducts (continued)

Entry	Ketone	Alkene	Conditions	Product	Yield[a] (%)
3	 **1c**	**2a**	THF, r.t., 5 d	 **3ac**	55
4	 **1d**	**2a**	THF, r.t., 3 d	 **3ad**	56
5	 **1e**	**2a**	neat, r.t., 24 h	 **3ae**	80
6	 **1f**	**2a**	neat, r.t., 24 h	 **3af**	74
7	**1a**	**2b**	THF, r.t., 5 d	 **3ba**	46
8	**1a**	**2b**	neat, r.t., 24 h	**3ba**	95
9	**1b**	**2b**	THF, r.t., 5 d	 **3bb**	37
10	**1e**	**2b**	neat, r.t., 0.5 h	 **3be**	94
11	**1f**	**2b**	neat, r.t., 12 h	 **3bf**	97
12	 **1g**	**2b**	THF, r.t., 10 d	 **3bg**	36
13	**1g**	**2b**	neat, r.t., 2 h	**3bg**	80

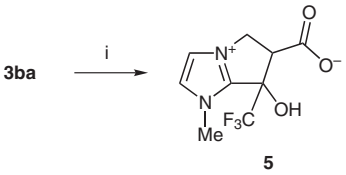
[a] The yields refer to isolated and purified products.

The use of excess **2b** led to the formation of compounds **4** through the Baylis–Hillman reaction of intermediates **3gb** with methyl acrylate (Scheme 2).

Spontaneous cyclization of imidazole derivatives **3ba** followed by ester hydrolysis afforded zwitterionic compound **5** in 39% yield (Scheme 3). Apparently spatial



Scheme 2 *Reagents and conditions*: (i) DABCO, r.t., 7 d.



Scheme 3 *Reagents and conditions*: (i) KOH, *i*-PrOH–H_2O, 60 °C, 2 h.

preorganization of the nucleophilic nitrogen atom of the imidazole ring and the highly polarized terminal double bond facilitates this cyclization.

Single crystal X-ray analysis unambiguously revealed the structure of compound **5** (Figure 1) as well as the formation of intramolecular hydrogen bond between the hydroxy and carboxy groups.

Compounds **3** readily reacted with various nucleophiles to give Michael addition products. The reaction with aniline **6a** occurred at 60 °C in methanol whereas thiophenol **6b** required suspended potassium hydroxide as base. In the case of phenol, a complex mixture of products was obtained which, according to LC-MS, contained ca. 40% of major compound **8**, which was isolated in 39% yield

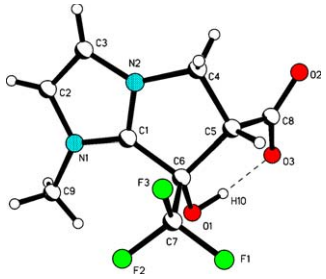
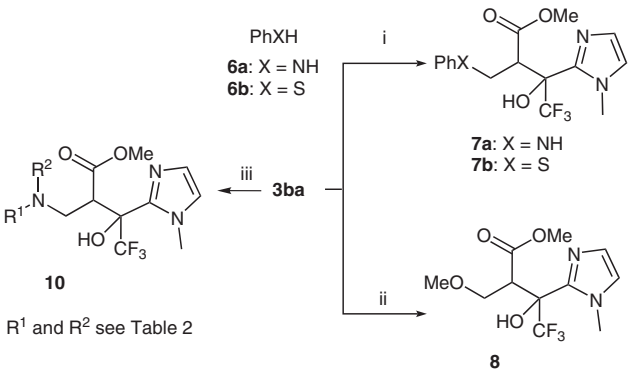


Figure 1 Molecular structure of compound **5**; the hydrogen bond is shown as a broken line.



Scheme 4 *Reagents and conditions*: (i) MeOH, 60 °C , 4 h; (ii) KOH, MeOH, 60 °C , 4 h; (iii) MeOH, r.t., 12 h.

(Scheme 4). The highest yields of the target compounds were attained in the case of the most reactive aliphatic amines **9a–f** and imidazole **9g** (Table 2).[5]

Table 2 Products of Michael Addition Reaction of **3aa** and **3ba**

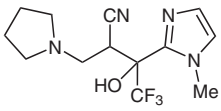
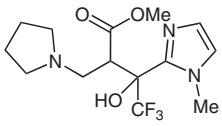
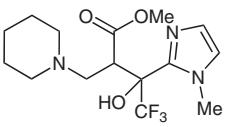
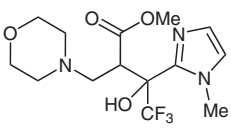
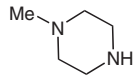
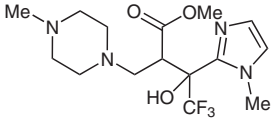
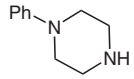
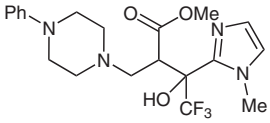
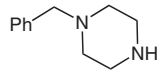
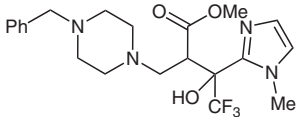
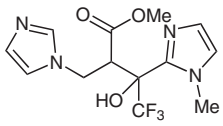
Entry	Amine	BH adduct	Product	Yield[a] (%)
1	 **9a**	**3aa**	 **10aa**	95
2	**9a**	**3ba**	 **10ab**	88
3	 **9b**	**3ba**	 **10bb**	66
4	 **9c**	**3ba**	 **10cb**	60

Table 2 Products of Michael Addition Reaction of **3aa** and **3ba** (continued)

Entry	Amine	BH adduct	Product	Yield[a] (%)
5	 **9d**	**3ba**	 **10db**	67
6	 **9e**	**3ba**	 **10eb**	83
7	 **9f**	**3ba**	 **10fb**	78
8	 **9g**	**3ba**	 **10gb**	72

[a] The yields refer to isolated and purified products.

The structures of all compounds obtained were confirmed by IR, ^{1}H, ^{13}C, and ^{19}F NMR, and APCI MS data and elemental analysis.

In conclusion, a simple method for the preparation of trifluoromethyl-containing allyl alcohols from 2-(trifluoroacetyl)-1,3-azoles through the Baylis–Hillman reaction was elaborated. We have shown that mild reaction conditions resulted in shorter reaction times and considerably higher yields than the described procedures for the Baylis–Hillman reaction. Compounds **3** readily undergo the Michael addition reaction to give novel functionally diverse druglike heterocycles.

Solvents and other chemicals were used as purchased. Starting materials were purchased (methyl acrylate, acrylonitrile, amines) or prepared (a set of 2-trifluoroacetyl-1,3-azoles).[3] Melting points were uncorrected. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker Avance drx 500 instrument at r.t. in DMSO-d_6. LC/MS spectra were recorded using an Agilent 1100 Series HPLC equipped with diode-matrix and mass-selective detector Agilent LC\MSD SL. The parameters of chromatography–mass analysis: column, Zorbax SB-C18, 1.8 μm, 4.6 mm × 15 mm; eluent A: MeCN–H_2O with 0.1% of TFA (95:5); eluent B: H_2O with 0.1% of TFA; flow rate, 3 mL/sec; volume of injected sample: 1 μL; UV-detectors at 215, 254, and 265 nm; ionization method: chemical ionization under atmospheric pressure (APCI); ionization mode: simultaneous scanning of positive and negative ions in the mass range of 80–1000 *m/z*. FT-IR spectra were recorded on a Nexus-470 spectrophotometer on samples prepared as KBr discs. Microanalyses were performed in the Microanalytical Laboratory of the Institute of Organic Chemistry, National Academy of Sciences of Ukraine. Satisfactory microanalyses were obtained for all new substances: C ±0.33; H ±0.45; N ±0.25.

Baylis–Hillman Adducts 3; General Procedure

To a stirred mixture of an appropriate ketone **1** (1.0 mmol), alkene **2** (1.0 mmol), and THF (1 mL) or without the solvent was added DABCO (0.15 mmol) and stirring continued at r.t. for the specified time. The solvent was removed in vacuo and the residue was washed with H_2O and crystallized (*i*-PrOH).

2-[2,2,2-Trifluoro-1-hydroxy-1-(1-methyl-1*H*-imidazol-2-yl)ethyl]acrylonitrile (3aa)

Colorless crystals; yield: 74%; mp 159–160 °C (dec.).

IR: 3620–3280 (br), 3151, 3132, 2979, 2732, 2233, 1631, 1540, 1485, 1392, 1290, 1240, 1213, 1174, 1157, 1109, 1001, 958, 924, 872, 775, 717, 685, 671 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 3.63 (s, 3 H), 6.23 (s, 1 H), 6.66 (s, 1 H), 6.92 (s, 1 H), 7.27 (s, 1 H), 8.25 (s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 34.68, 75.17 (q, $^2J_{CF}$ = 29.3 Hz), 116.38, 120.60, 124.14 (q, $^1J_{CF}$ = 288.0 Hz), 125.38, 127.03, 137.80, 140.17.

^{19}F NMR (DMSO-d_6): δ = –75.51.

MS (APCI): *m/z* = 232 [M + 1].

2-[1-(1-Allyl-1*H*-imidazol-2-yl)-2,2,2-trifluoro-1-hydroxyethyl]acrylonitrile (3ab)

Colorless crystals; yield: 62%; mp 127–128 °C.

IR: 3630–3290 (br), 3153, 3116, 2993, 2742, 2642, 2229, 1649, 1620, 1475, 1416, 1402, 1286, 1267, 1201, 1186, 1164, 1142, 1117, 993, 962, 924, 865, 835, 764, 744, 715 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 4.67 (m, 2 H), 5.15 (d, J = 17.0 Hz, 1 H), 5.21 (d, J = 10.5 Hz, 1 H), 5.92 (m, 1 H), 6.28 (s, 1 H), 6.65 (s, 1 H), 6.98 (s, 1 H), 7.25 (s, 1 H), 8.36 (s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 49.31, 75.24 (q, $^2J_{CF}$ = 29.8 Hz), 116.34, 118.64, 120.85, 123.61, 124.06 (q, $^1J_{CF}$ = 288.4 Hz), 127.61, 133.87, 137.81, 140.03.

^{19}F NMR (DMSO-d_6): δ = –75.40.

MS (APCI): m/z = 258 [M + 1].

2-[1-(1-Butyl-1*H*-imidazol-2-yl)-2,2,2-trifluoro-1-hydroxyethyl]acrylonitrile (3ac)
Colorless crystals; yield: 55%; mp 134–135 °C.

IR: 3640–3220 (br), 3156, 3134, 2958, 2933, 2875, 2719, 2675, 2623, 2567, 2231, 1621, 1483, 1458, 1396, 1381, 1294, 1242, 1174, 1105, 1005, 960, 926, 874, 773, 746, 710, 677 cm^{-1}.

^{1}H NMR (DMSO-d_6): d = 0.88 (t, J = 7.0 Hz, 3 H), 1.27 (m, 2 H), 1.69 (m, 2 H), 3.96 (m, 2 H), 6.25 (s, 1 H), 6.68 (s, 1 H), 6.94 (s, 1 H), 7.35 (s, 1 H), 8.25 (s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 13.94, 19.85, 32.57, 46.59, 75.28 (q, $^2J_{CF}$ = 28.9 Hz), 116.28, 121.18, 123.36, 124.11 (q, $^1J_{CF}$ = 288.4 Hz), 127.44, 137.63, 140.03.

^{19}F NMR (DMSO-d_6): δ = –75.34.

MS (APCI): m/z = 274 [M + 1].

MS (IE): m/z (%) = 273 (8) [M]$^+$, 205 (15), 204 (100) [M – CF_3]$^+$, 165 (15), 148 (96), 95 (14), 81 (13), 57 (16), 55 (11), 41 (32).

2-[1-(5-Chloro-1-methyl-1*H*-imidazol-2-yl)-2,2,2-trifluoro-1-hydroxyethyl]acrylonitrile (3ad)
Colorless crystals; yield: 56%; mp 128–129 °C.

IR: 3600–2930 (br), 2754, 2708, 2229, 1655, 1525, 1473, 1450, 1400, 1358, 1279, 1205, 1192, 1182, 1134, 1107, 999, 980, 972, 916, 877, 833, 748, 727, 700, 640 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 3.57 (s, 3 H), 6.31 (s, 1 H), 6.72 (s, 1 H), 7.11 (s, 1 H), 8.44 (s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 32.32, 75.29 (q, $^2J_{CF}$ = 29.8 Hz), 116.19, 119.90, 120.70, 123.89 (q, $^1J_{CF}$ = 288.4 Hz), 124.39, 138.57, 140.50.

^{19}F NMR (DMSO-d_6): δ = –75.39.

MS (APCI): m/z = 266 [M + 1].

2-[2,2,2-Trifluoro-1-hydroxy-1-(1-methyl-1*H*-1,2,4-triazol-5-yl)ethyl]acrylonitrile (3ae)
Colorless crystals; yield: 80%; mp 129–130 °C.

IR: 3630–3305 (br), 3124, 2924, 2769, 2723, 2237, 1630, 1491, 1458, 1439, 1408, 1389, 1281, 1248, 1190, 1115, 1001, 984, 941, 908, 879, 731, 706, 675 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 3.88 (s, 3 H), 6.40 (s, 1 H), 6.77 (s, 1 H), 8.05 (s, 1 H), 8.74 (s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 37.91, 74.36 (q, $^2J_{CF}$ = 30.2 Hz), 115.90, 119.13, 123.72 (q, $^1J_{CF}$ = 288.0 Hz), 138.93, 148.90, 150.27.

^{19}F NMR (DMSO-d_6): δ = –75.74.

MS (APCI): m/z = 231 [M – 1].

2-[2,2,2-Trifluoro-1-hydroxy-1-(4-methylthiazol-2-yl)ethyl]acrylonitrile (3af)
Yellow oil: yield: 74%.

IR: 3600–3170 (br), 3120, 2931, 2237, 1659, 1527, 1446, 1396, 1273, 1244, 1190, 1174, 1126, 1092, 968, 893, 872, 746 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 2.40 (s, 3 H), 6.57 (s, 1 H), 6.70 (s, 1 H), 7.49 (s, 1 H), 8.76 (s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 17.32, 76.69 (q, $^2J_{CF}$ = 30.2 Hz), 116.41, 117.80, 120.67, 123.65 (q, $^1J_{CF}$ = 288.0 Hz), 137.97, 153.25, 165.00.

^{19}F NMR (DMSO-d_6): δ = –81.41.

MS (APCI): m/z = 249 [M + 1].

Methyl 2-[2,2,2-Trifluoro-1-hydroxy-1-(1-methyl-1*H*-imidazol-2-yl)ethyl]acrylate (3ba)
Colorless crystals; yield: 95%; mp 106–107 °C.

IR: 3560–3300 (br), 3155, 3124, 3020, 2966, 2726, 2663, 2588, 1736, 1631, 1535, 1481, 1446, 1389, 1321, 1269, 1250, 1184, 1171, 1130, 1113, 1103, 1055, 999, 960, 949, 920, 856, 814, 760, 733, 710, 690, 665, 627, 596 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 3.56 (s, 3 H), 3.58 (s, 3 H), 6.18 (s, 1 H), 6.43 (s, 1 H), 6.81 (s, 1 H), 7.12 (s, 1 H), 7.57 (s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 34.32, 52.50, 75.14 (q, $^2J_{CF}$ = 28.9 Hz), 124.11, 124.56 (q, $^1J_{CF}$ = 288.0 Hz), 126.26, 129.34, 137.67, 141.99, 165.33.

^{19}F NMR (DMSO-d_6): δ = –74.88.

MS (APCI): m/z = 265 [M + 1].

Methyl 2-[1-(1-Allyl-1*H*-imidazol-2-yl)-2,2,2-trifluoro-1-hydroxyethyl]acrylate (3bb)
Colorless crystals; yield: 37%; mp 103–104 °C.

IR: 3600–3200 (br), 3155, 3131, 3028, 2958, 2804–2495 (br), 1741, 1630, 1477, 1444, 1392, 1321, 1267, 1169, 1105, 1001, 958, 920, 812, 760, 671 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 3.53 (s, 3 H), 4.63 (m, 2 H), 5.13 (m, 2 H), 5.88 (s, 1 H), 6.20 (s, 1 H), 6.45 (s, 1 H), 6.85 (s, 1 H), 7.07 (s, 1 H), 7.64 (s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 49.09, 52.42, 75.30 (q, $^2J_{CF}$ = 28.9 Hz), 118.07, 122.31, 124.516 (q, $^1J_{CF}$ = 288.0 Hz), 126.92, 129.66, 134.44, 137.80, 141.81, 165.10.

^{19}F NMR (DMSO-d_6): δ = –75.19.

MS (APCI): m/z = 291 [M + 1].

Methyl 2-[2,2,2-Trifluoro-1-hydroxy-1-(1-methyl-1*H*-1,2,4-triazol-5-yl)ethyl]acrylate (3be)
Colorless crystals; yield: 94%; mp 75–76 °C.

IR: 3600–3300 (br), 3140, 3124–2980 (br), 2964, 2777, 1736, 1630, 1506, 1466, 1456, 1443, 1385, 1321, 1271, 1194, 1182, 1161, 1119, 1026, 1001, 962, 931, 899, 858, 816, 787, 715, 671, 588 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 3.56 (s, 3 H), 3.80 (s, 3 H), 6.38 (s, 1 H), 6.58 (s, 1 H), 7.87 (s, 1 H), 8.05 (br s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 37.35, 52.59, 74.18 (q, $^2J_{CF}$ = 30.2 Hz), 124.19 (q, $^1J_{CF}$ = 288.0 Hz), 130.60, 136.30, 149.51, 150.57, 164.71.

^{19}F NMR (DMSO-d_6): δ = –75.15.

MS (APCI): m/z = 266 [M + 1].

Methyl 2-[2,2,2-Trifluoro-1-hydroxy-1-(4-methylthiazol-2-yl)ethyl]acrylate (3bf)
Colorless oil; yield: 97%.

IR: 3600–3150 (br), 3120, 2958, 2929, 2856, 1733, 1693, 1618, 1529, 1443, 1329, 1265, 1194, 1173, 1136, 980, 962, 885, 818, 744, 619 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 2.31 (s, 3 H), 3.55 (s, 3 H), 6.22 (s, 1 H), 6.48 (s, 1 H), 7.33 (s, 1 H), 8.01 (br s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 17.29, 52.44, 77.05 (q, $^2J_{CF}$ = 28.9 Hz), 116.77, 124.21 (q, $^1J_{CF}$ = 288.0 Hz), 129.40, 137.48, 152.10, 164.96, 167.73.

^{19}F NMR (DMSO-d_6): δ = –73.89.

MS (APCI): *m*/*z* = 282 [M + 1].

Methyl 2-[1-(Benzothiazol-2-yl)-2,2,2-trifluoro-1-hydroxyethyl]acrylate (3bg)

Colorless crystals; yield: 80%; mp 45–46 °C.

IR: 3250 (br), 3140, 2958, 2926, 2854, 1695, 1616, 1514, 1444, 1417, 1325, 1259, 1186, 1176, 1149, 995, 968, 904, 831, 818, 766, 741, 731, 634 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 3.54 (s, 3 H), 6.37 (s, 1 H), 6.63 (s, 1 H), 7.47 (dd, *J* = 8.0, 7.0 Hz, 1 H), 7.52 (dd, *J* = 8.0, 7.0 Hz, 1 H), 8.02 (d, *J* = 8.0 Hz, 1 H), 8.13 (d, *J* = 8.0 Hz, 1 H), 8.32 (s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 52.52, 77.54 (q, $^2J_{CF}$ = 28.9 Hz), 122.68, 123.64, 124.27 (q, $^1J_{CF}$ = 288.0 Hz), 126.08, 126.66, 130.02, 135.63, 137.13, 152.84, 164.61, 170.92.

^{19}F NMR (DMSO-d_6): δ = –74.94.

MS (APCI): *m*/*z* = 318 [M + 1].

Dimethyl 2-[1-(Benzothiazol-2-yl)-2,2,2-trifluoro-1-hydroxyethyl]-4-methylenepentanedioate (4)

Colorless crystals; yield: 40%; mp 122–123 °C.

IR: 3340 (br), 3078, 3001, 2951, 2855, 1727, 1698, 1635, 1502, 1446, 1438, 1378, 1340, 1317, 1294, 1251, 1236, 1188, 1170, 1141, 1033, 960, 893, 819, 765, 735, 685, 607 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 2.80–2.93 (m, 2 H), 3.25 (s, 3 H), 3.70 (s, 3 H), 3.80 (m, 1 H), 5.62 (s, 1 H), 6.10 (s, 1 H), 7.46 (dd, *J* = 8.0, 7.0 Hz, 1 H), 7.52 (dd, *J* = 8.0, 7.0 Hz, 1 H), 8.04 (d, *J* = 8.0 Hz, 1 H), 8.12 (d, *J* = 8.0 Hz, 1 H), 8.13 (s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 29.57, 50.73, 51.84, 52.46, 78.31 (q, $^2J_{CF}$ = 28.1 Hz), 122.74, 123.67, 124.60 (q, $^1J_{CF}$ = 289.2 Hz), 126.14, 126.86, 128.12, 135.10, 137.00, 153.27, 166.58, 170.11, 170.97.

^{19}F NMR (DMSO-d_6): δ = –74.84.

MS (APCI): *m*/*z* = 404 [M + 1].

7-Hydroxy-1-methyl-7-(trifluoromethyl)-1,5,6,7-tetrahydropyrrolo[1,2-*a*]imidazol-4-ium-6-carboxylate (5)

Compound **3ba** (3 mmol) was dissolved in *i*-PrOH (2 mL), a soln of KOH (0.1 mmol) in H_2O (1 mL) was added. The mixture was stirred at 60 °C for 2 h. The solvent was removed in vacuo, the residue was recrystallized (*i*-PrOH) to give **5** as colorless crystals; yield: 39%; mp 206–207 °C (dec).

IR: 3650–3200 (br), 3109, 3043, 3020, 2980, 1578, 1460, 1441, 1363, 1313, 1250, 1203, 1169, 1149, 1070, 987, 947, 818, 687, 623, 588, 519, 449 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 3.50 (d, *J* = 8.0 Hz, 1 H), 3.88 (s, 3 H), 4.49 (dd, *J* = 11.5, 8.0 Hz, 1 H), 4.75 (d, *J* = 11.5 Hz, 1 H), 7.81 (s, 1 H), 7.82 (s, 1 H), 13.99 (s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 34.91, 46.38, 50.89, 77.28 (q, $^2J_{CF}$ = 31.9 Hz), 119.84, 124.85 (q, $^1J_{CF}$ = 285.5 Hz), 129.92, 145.61, 170.44.

^{19}F NMR (DMSO-d_6): δ = –79.91.

MS (APCI): *m*/*z* = 251 [M+1].

Methyl 2-(Anilinomethyl)-4,4,4-trifluoro-3-hydroxy-3-(1-methyl-1*H*-imidazol-2-yl)butanoate (7a)

A mixture of aniline (1.0 mmol), **3ba** (1.0 mmol), and MeOH (1 mL) was stirred at 60 °C for 4 h. The solvent was removed in vacuo, the residue was recrystallized (*i*-PrOH) to give **7a** as colorless crystals; yield: 38%; mp 152–153 °C.

IR: 3367 (br), 3257, 3140, 3118, 3055, 3035, 3010, 2956, 2927, 2872, 1711, 1605, 1539, 1500, 1485, 1470, 1439, 1383, 1356, 1300, 1269, 1238, 1209, 1196, 1173, 1130, 982, 964, 906, 750, 708, 692, 592, 575 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 2.96 (m, 1 H), 3.56 (m, 1 H), 3.60 (s, 3 H), 3.82 (s, 3 H), 4.01 (m, 1 H), 5.73 (m, 1 H), 6.51 (t, *J* = 7.5 Hz, 1 H), 6.66 (d, *J* = 7.5 Hz, 2 H), 6.93 (s, 1 H), 6.99 (s, 1 H), 7.03 (dd, *J* = 7.5 Hz, 2 H), 7.20 (s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 35.90, 42.61, 48.88, 52.27, 77.75 (q, $^2J_{CF}$ = 28.5 Hz), 112.77, 116.46, 124.97 (q, $^1J_{CF}$ = 288.0 Hz), 125.64, 127.15, 129.27, 140.78, 148.97, 171.63.

^{19}F NMR (DMSO-d_6): δ = –76.34.

MS (APCI): *m*/*z* = 358 [M + 1].

Methyl 4,4,4-Trifluoro-3-hydroxy-3-(1-methyl-1*H*-imidazol-2-yl)-2-[(phenylsulfanyl)methyl]butanoate (7b)

A mixture of PhSH (1.0 mmol), KOH (0.1 mmol), **3ba** (1.0 mmol), and MeOH (1 mL) was stirred at 60 °C for 4 h. CH_2Cl_2 was added, the organic phase was washed with H_2O and concentrated in vacuo. Product was purified by flash chromatography to give **7b** as a colorless oil; yield: 49%.

IR: 3600–3200 (br), 3114, 3059, 3005, 2954, 1713, 1583, 1524, 1483, 1441, 1352, 1279, 1217, 1165, 1122, 1088, 1054, 1026, 1011, 964, 901, 833, 744, 690, 652 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 2.96 (d, *J* = 13.5 Hz, 1 H), 3.20 (dd, *J* = 13.5, 12.0 Hz, 1 H), 3.62 (s, 3 H), 3.79 (s, 3 H), 3.89 (d, *J* = 12.0 Hz, 1 H), 6.95 (s, 1 H), 7.16 (s, 1 H), 7.17–7.23 (m, 2 H), 7.28–7.38 (m, 4 H).

^{13}C NMR (DMSO-d_6): δ = 31.29, 35.78, 49.99, 52.32, 78.42 (q, $^2J_{CF}$ = 28.9 Hz), 124.77 (q, $^1J_{CF}$ = 288.0 Hz), 125.77, 126.54, 127.20, 128.84, 129.49, 135.39, 140.45, 170.66.

^{19}F NMR (DMSO-d_6): δ = –76.08.

MS (APCI): *m*/*z* = 375 [M + 1].

Methyl 4,4,4-Trifluoro-3-hydroxy-2-(methoxymethyl)-3-(1-methyl-1*H*-imidazol-2-yl)butanoate (8)

A mixture of **3ba** (1.0 mmol), KOH (1.0 mmol), and MeOH (1 mL) was stirred at 60 °C for 4 h. The solvent was removed in vacuo, the residue was recrystallized (*i*-PrOH) to give **8** as colorless crystals; yield: 39%; mp 79–80 °C.

IR: 3670–3150 (br), 3138, 3003, 2956, 2918, 1740, 1484, 1439, 1360, 1290, 1242, 1209, 1188, 1163, 1120, 1068, 995, 966, 941, 914, 764, 712, 661 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 3.14 (s, 3 H), 3.27 (dd, *J* = 9.5, 3.0 Hz, 1 H), 3.63 (s, 3 H), 3.70 (dd, *J* = 10.5, 9.5 Hz, 1 H), 3.76 (s, 3 H), 3.85 (dd, *J* = 10.5, 3.0 Hz, 1 H), 6.90 (s, 1 H), 6.97 (s, 1 H), 7.16 (s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 35.77, 49.77, 52.25, 58.72, 70.76, 77.10 (q, $^2J_{CF}$ = 28.9 Hz), 124.81 (q, $^1J_{CF}$ = 288.4 Hz), 125.45, 127.13, 140.47, 171.20.

^{19}F NMR (DMSO-d_6): δ = –76.40.

MS (APCI): *m*/*z* = 297 [M + 1].

Michael Addition of Secondary Amines; General Procedure

A mixture of amine (1.0 mmol), **3** (1.0 mmol), and MeOH (1 mL) was stirred at r.t. for 12 h. The solvent was removed in vacuo, the residue was recrystallized (*i*-PrOH).

4,4,4-Trifluoro-3-hydroxy-3-(1-methyl-1*H*-imidazol-2-yl)-2-(pyrrolidin-1-ylmethyl)butanenitrile (10aa)

Colorless crystals; yield: 95%; mp 131 °C.

IR: 3670–3170 (br), 3124, 2941, 2864, 2243, 1473, 1408, 1348, 1254, 1184, 1155, 1136, 1119, 1003, 976, 947, 906, 887, 756, 685, 453 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 1.68 (m, 4 H), 2.39 (m, 2 H), 2.46 (m, 1 H), 2.60 (m, 2 H), 3.09 (m, 1 H), 3.79 (s, 3 H), 4.13 (m, 1 H), 6.91 (s, 1 H), 7.19 (s, 1 H), 8.47 (s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 23.71, 35.65, 36.40, 54.14, 54.44, 77.58 (q, $^2J_{CF}$ = 28.9 Hz), 118.93, 124.52 (q, $^1J_{CF}$ = 288.0 Hz), 125.80, 127.19, 140.00.

^{19}F NMR (DMSO-d_6): δ = –75.52.

MS (APCI): *m*/*z* = 303 [M + 1].

Methyl 4,4,4-Trifluoro-3-hydroxy-3-(1-methyl-1*H*-imidazol-2-yl)-2-(pyrrolidin-1-ylmethyl)butanoate (10ab)
Colorless crystals; yield: 88%; mp 115–116 °C.

IR: 3650–3170 (br), 3154, 3106, 3026, 2968, 2879, 2827, 2783, 2748, 1743, 1730, 1529, 1479, 1444, 1437, 1356, 1284, 1176, 1138, 1117, 1055, 987, 962, 951, 931, 906, 889, 791, 764, 712, 687, 588, 548, 509, 498 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 1.60 (m, 4 H), 2.12 (d, *J* = 10.5 Hz, 1 H), 2.27 (m, 2 H), 2.46 (m, 2 H), 3.09 (dd, *J* = 10.5, 9.5 Hz, 1 H), 3.61 (s, 3 H), 3.78 (s, 3 H), 3.84 (d, *J* = 9.5 Hz, 1 H), 6.88 (s, 1 H), 6.98 (s, 1 H), 7.13 (s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 23.65, 35.78, 48.74, 52.10, 54.08, 54.68, 77.86 (q, $^2J_{CF}$ = 28.9 Hz), 124.97 (q, $^1J_{CF}$ = 288.0 Hz), 125.23, 127.03, 140.86, 171.99.

^{19}F NMR (DMSO-d_6): δ = –76.26.

MS (APCI): *m*/*z* = 336 [M + 1].

Methyl 4,4,4-Trifluoro-3-hydroxy-3-(1-methyl-1*H*-imidazol-2-yl)-2-(piperidin-1-ylmethyl)butanoate (10bb)
Colorless crystals; yield: 66%; mp 101–102 °C.

IR: 3630–3150 (br), 2937, 2852, 1743, 1732, 1477, 1437, 1363, 1304, 1284, 1200, 1167, 1130, 1057, 968, 931, 906, 762, 669, 417 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 1.30 (m, 2 H), 1.38 (m, 4 H), 2.09 (m, 2 H), 2.15 (d, *J* = 11.5 Hz, 1 H), 2.43 (m, 2 H), 2.79 (dd, *J* = 11.5 Hz, 1 H), 3.61 (s, 3 H), 3.77 (s, 3 H), 3.85 (d, *J* = 11.5 Hz, 1 H), 6.88 (s, 1 H), 7.05 (s, 1 H), 7.13 (s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 24.27, 26.14, 35.75, 47.20, 52.03, 54.69, 57.20, 77.73 (q, $^2J_{CF}$ = 28.9 Hz), 124.97 (q, $^1J_{CF}$ = 288.0 Hz), 125.22, 127.01, 140.81, 172.03.

^{19}F NMR (DMSO-d_6): δ = –76.27.

MS (APCI): *m*/*z* = 350 [M + 1].

Methyl 4,4,4-Trifluoro-3-hydroxy-3-(1-methyl-1*H*-imidazol-2-yl)-2-(morpholin-4-ylmethyl)butanoate (10cb)
Colorless crystals; yield: 60%; mp 118–119 °C.

IR: 3670–3190 (br), 3118, 3097, 2999, 2954, 2877, 2852, 2827, 2777, 2688, 1724, 1524, 1485, 1439, 1360, 1338, 1296, 1244, 1211, 1196, 1176, 1142, 1117, 984, 964, 930, 914, 901, 876, 793, 712, 673, 552, 457 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 2.05–2.19 (m, 3 H), 2.40–2.47 (m, 2 H), 2.84 (dd, *J* = 11.8 Hz, 1 H), 3.37–3.54 (m, 4 H), 3.63 (s, 3 H), 3.77 (s, 3 H), 3.90 (dd, *J* = 11.0, 3.5 Hz, 1 H), 6.87 (s, 1 H), 6.89 (s, 1 H), 7.14 (s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 35.84, 47.14, 52.16, 53.92, 57.05, 66.73, 77.62 (q, $^2J_{CF}$ = 28.5 Hz), 124.96 (q, $^1J_{CF}$ = 288.0 Hz), 125.39, 127.10, 140.69, 171.89.

^{19}F NMR (DMSO-d_6): δ = –76.36.

MS (APCI): *m*/*z* = 352 [M + 1].

Methyl 4,4,4-Trifluoro-3-hydroxy-3-(1-methyl-1*H*-imidazol-2-yl)-2-[(4-methylpiperazin-1-yl)methyl]butanoate (10db)
Colorless crystals; yield: 67%; mp 106–107 °C.

IR: 3670–3150 (br), 3097, 2966, 2953, 2931, 2883, 2848, 2829, 2802, 2775, 1724, 1524, 1479, 1456, 1439, 1356, 1336, 1288, 1252, 1221, 1194, 1174, 1130, 1092, 1012, 985, 962, 928, 901, 870, 812, 785, 679, 621, 567 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 2.05 (s, 3 H), 2.11–2.30 (m, 6 H), 2.42–2.52 (m, 2 H), 2.84 (dd, *J* = 11.8 Hz, 1 H), 3.62 (s, 3 H), 3.77 (s, 3 H), 3.86 (m, 1 H), 6.88 (s, 1 H), 6.39 (s, 1 H), 7.13 (s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 35.81, 46.08, 47.31, 52.09, 53.26, 55.22, 56.48, 77.68 (q, $^2J_{CF}$ = 28.5 Hz), 124.97 (q, $^1J_{CF}$ = 288.0 Hz), 125.31, 127.09, 140.74, 171.95.

^{19}F NMR (DMSO-d_6): δ = –76.36.

MS (APCI): *m*/*z* = 365 [M + 1].

Methyl 4,4,4-Trifluoro-3-hydroxy-3-(1-methyl-1*H*-imidazol-2-yl)-2-[(4-phenylpiperazin-1-yl)methyl]butanoate (10eb)
Colorless crystals; yield: 83%; mp 113–114 °C.

IR: 3670–3140 (br), 2960, 2854, 2812, 1724, 1603, 1504, 1481, 1446, 1387, 1354, 1279, 1261, 1238, 1169, 1122, 1011, 984, 953, 931, 764, 692, 675, 517 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 2.21 (m, 1 H), 2.30 (m, 2 H), 2.63 (m, 2 H), 2.93 (dd, *J* = 12.0 Hz, 1 H), 3.02 (m, 4 H), 3.63 (s, 3 H), 3.78 (s, 3 H), 3.94 (m, 1 H), 6.74 (t, *J* = 7.0 Hz, 1 H), 6.85–6.95 (m, 4 H), 7.13–7.22 (m, 3 H).

^{13}C NMR (DMSO-d_6): δ = 35.84, 47.37, 48.78, 52.14, 53.35, 56.56, 77.67 (q, $^2J_{CF}$ = 28.5 Hz), 115.79, 119.24, 124.99 (q, $^1J_{CF}$ = 288.0 Hz), 125.37, 127.13, 129.30, 140.74, 151.41, 172.00.

^{19}F NMR (DMSO-d_6): δ = –76.34.

MS (APCI): *m*/*z* = 427 [M + 1].

Methyl 2-[(4-Benzylpiperazin-1-yl)methyl]-4,4,4-trifluoro-3-hydroxy-3-(1-methyl-1*H*-imidazol-2-yl)butanoate (10fb)
Colorless crystals; yield: 78%; mp 117–118 °C.

IR: 3650–3160 (br), 3086, 3032, 2947, 2810, 2767, 1741, 1477, 1456, 1437, 1362, 1294, 1286, 1201, 1165, 1122, 1012, 966, 933, 904, 760, 741, 696 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 2.10–2.39 (m, 7 H), 2.50–2.52 (m, 2 H), 2.84 (dd, *J* = 12.0 Hz, 1 H), 3.40 (m, 2 H), 3.61 (s, 3 H), 3.77 (s, 3 H), 3.86 (m, 1 H), 6.88 (s, 1 H), 6.94 (s, 1 H), 7.13 (s, 1 H), 7.18–7.33 (m, 5 H).

^{13}C NMR (DMSO-d_6): δ = 35.78, 47.29, 52.08, 53.13, 53.43, 56.54, 62.45, 77.68 (q, $^2J_{CF}$ = 27.7 Hz), 124.97 (q, $^1J_{CF}$ = 288.0 Hz), 125.29, 127.05, 127.27, 128.53, 129.18, 138.67, 140.73, 171.94.

^{19}F NMR (DMSO-d_6): δ = –76.30.

MS (APCI): *m*/*z* = 441 [M + 1].

Methyl 4,4,4-Trifluoro-3-hydroxy-2-(1*H*-imidazol-1-ylmethyl)-3-(1-methyl-1*H*-imidazol-2-yl)butanoate (10gb)
Colorless crystals; yield: 72%; mp 131–132 °C.

IR: 3610, 3500–3300 (br), 3259, 3136, 3116, 2954, 1732, 1514, 1479, 1435, 1360, 1275, 1252, 1219, 1169, 1136, 1107, 1092, 987, 966, 947, 763, 660 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 3.54 (s, 3 H), 3.82 (s, 3 H), 3.95 (d, *J* = 12.0 Hz, 1 H), 4.09 (d, *J* = 11.0 Hz, 1 H), 4.41 (dd, *J* = 12.0, 11.0 Hz, 1 H), 6.87 (s, 1 H), 7.00 (s, 1 H), 7.01 (s, 1 H), 7.24 (s, 1 H), 7.44 (s, 1 H), 7.51 (br s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 35.85, 45.77, 51.96, 52.66, 77.60 (q, $^2J_{CF}$ = 30.2 Hz), 119.50, 124.69 (q, $^1J_{CF}$ = 288.0 Hz), 125.98, 127.44, 129.35, 137.85, 140.24, 170.38.

^{19}F NMR (DMSO-d_6): δ = –76.01.

MS (APCI): *m*/*z* = 333 [M + 1].

Single crystal X-ray analysis: Unit cell parameters and intensities of all sets of reflections were measured using an Xcalibur-3 diffractometer (CCD detector, λ(MoKα) irradiation, ω-scans) All structures were solved by direct method using the SHELXTL package.[6] The positions of the hydrogen atoms were located from difference maps of the electron density and refined as riding atoms. Atomic coordinates and crystallographic parameters were deposited at the Cambridge Crystallographic Data Centre under CCDC 687052.

Crystal data for **5**: $C_9H_9F_3N_2O_3$, triclinic, $P\bar{1}$, a = 6.619(2) Å, b = 8.654(5) Å, c = 10.160(3) Å, α = 107.15(4)°, β = 92.01(2)°, γ = 111.11(4)°, V = 512.2(4) Å^3, Z = 2, ρ_{calcd} = 1.62 g/cm^3, μ = 0.156 mm^{-1}, F(000) = 256, 159 parameters, $R1$ = 0.0317, $wR2$ = 0.0791 (1284 reflections. $F > 4\sigma$), $R1$ = 0.0451, $wR2$ = 0.0842 (1702 unique reflections), S = 0.987, Δρ (min/max) = –0.202/ 0.191 e Å^{-3}.

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