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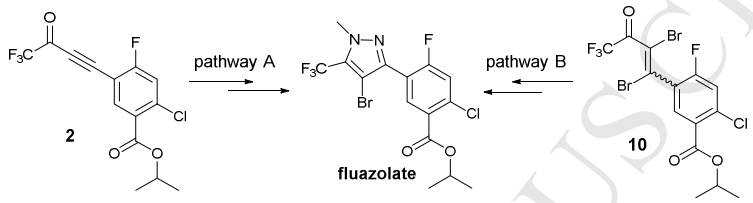

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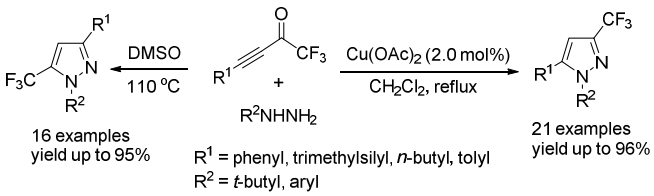
ABSTRACT

Starting from commercially available 2-chloro-4-fluorobenzoic acid **4**, synthesis of fluazolate was achieved in up to 30% overall yield via the key procedure of either regioselective [3+2] cyclocondensation of trifluoromethyl-α,β-ynone **2** with hydrazine hydrate or nucleophilic substitution-cyclization of trifluoromethyl-α,β-dibromoenone **10** with hydrazine hydrate.

1. Introduction

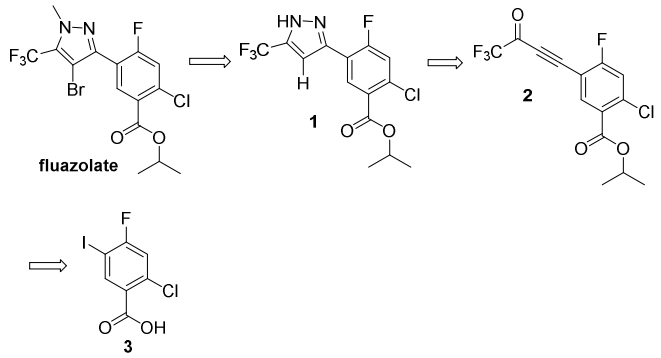
The 3- and 5-trifluoromethylpyrazole substructures are commonly present in many pharmaceuticals and biologically active compounds, including the non-steroidal anti-inflammatory drug celecoxib,[1] anticancer agent SC-560,[2] anti-viral agent AS-136A,[3] anticoagulant drug razaxaban,[4] insecticide DP-23[5] and herbicide fluazolate.[6] Generally, 3- or 5-trifluoromethylpyrazole derivatives are prepared via the condensation of 1,1,1-trifluoromethyl-1,3-diketones, or their synthetic equivalents, with hydrazines.[7] However, when applied to pharmaceutical manufacturing, these methods often suffer from limitations, such as low functional-group tolerance and formation of unwanted regioisomers. Recently, we developed a highly facile methodology for the regioselective synthesis of 3- and 5-trifluoromethylpyrazole compounds via the [3+2] cyclocondensation of trifluoromethyl-α,β-ynones with hydrazines.[8] As shown in Scheme 1, the regioselectivity resulting from these reactions can be readily shifted via minor modifications to the reaction procedures to preferentially produce either 3- or 5-trifluoromethylpyrazole products. The synthetic procedure is operationally very simple. Yields of products are generally excellent, and the tolerance of functionality is high. These features render it an attractive alternative to existing methods.

Fluazolate (JV-485), developed by Monsanto and Bayer AG, is a protoporphyrinogen IX oxidase-inhibiting herbicide used on winter wheat. The commercial route to this product consists of two key steps: a classic cyclization reaction of the 1,1,1-trifluoromethyl-1,3-diketone intermediate with hydrazine and a



Scheme 1. [3+2] cyclocondensation reaction for the selective synthesis of 3- and 5-trifluoromethylpyrazoles

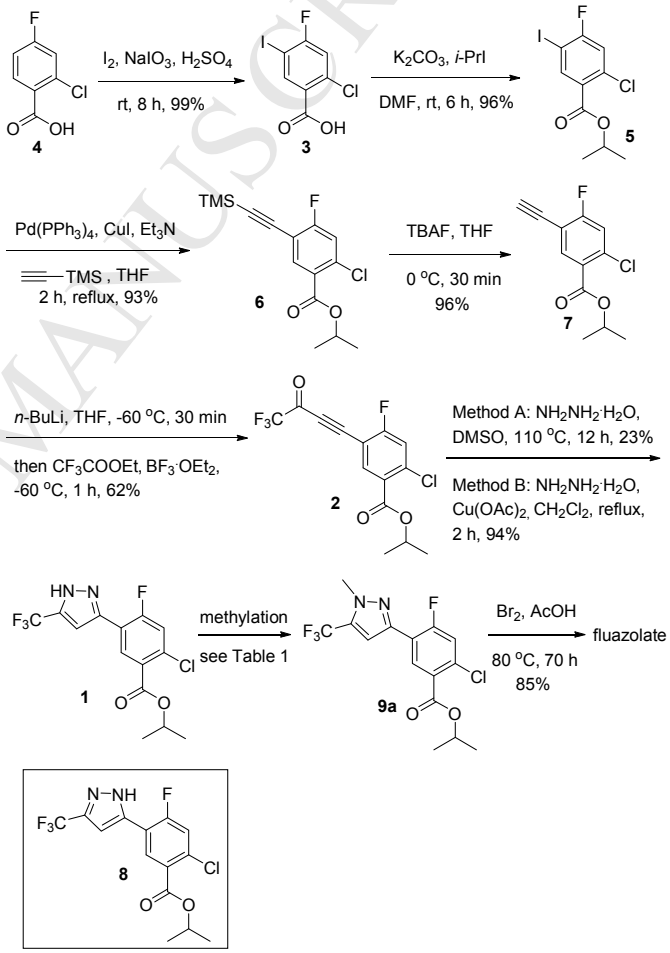
regioselective *N*-methylation reaction.[9] Alternatively, Harrity et al. reported a formal synthesis of fluazolate whereby the 5-trifluoromethylpyrazole core structure could be accessed through reaction of 4-trifluoromethylsydnone with a suitable alkyne.[10] In continuation of our efforts to synthesize biologically active trifluoromethylpyrazole compounds, we expanded the aforementioned regioselective [3+2] cyclocondensation, modifying the trifluoromethyl-α,β-ynone intermediate, to expedite the preparation of fluazolate. The retrosynthesis of fluazolate is depicted in Scheme 2. The target molecule is anticipated to be achieved from the advanced intermediate **1**, the synthesis of which will proceed from trifluoromethyl-α,β-ynone **2** via [3+2] cyclocondensation with hydrazine. A more straightforward pathway which using *N*-methylhydrazine in the [3+2] cyclocondensation is not preferred because that compound is highly toxic and carcinogenic. Compound **2** is proposed to be prepared from compound **3** via a synthetic sequence of isopropyl esterification followed by a Sonogashira coupling reaction.



Scheme 2 The retrosynthesis of fluazolate

2. Results and discussion

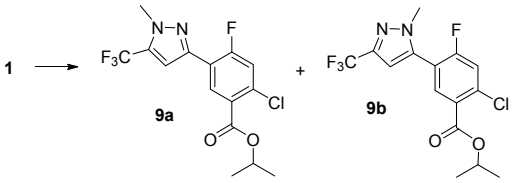
Our endeavor to synthesize fluazolate began with synthesis of compound **3**. Thus, starting with commercially available compound **4** and treating it with iodine in the presence of sodium iodate gave the required compound **3** in quantitative yield (99%). Esterification of compound **3**, giving compound **5**, was readily achieved by treating **3** with isopropyl iodide in the presence of potassium carbonate in DMF. To incorporate the trifluoromethyl ynone functionality into **5**, the procedures involving the coupling reaction of 1,1,1-trifluoro-4-(trimethylstannyl)but-3-yn-2-one[11] with compound **5** were initially examined. Unfortunately, all attempts failed to directly convert compound **5** to **2**. In another approach, a trimethylsilyl acetylene group was introduced by a typical Sonogashira cross-coupling reaction,[12] wherein compound **5** was mixed with trimethylsilyl acetylene, CuI and $Pd(PPh_3)_4$ in THF to produce the desired compound **6** in 93% yield, which in turn underwent desilylation using TBAF in THF to give compound **7** in a virtually quantitative yield (96%). Treatment of compound **7** with *n*-BuLi at -60 °C in THF was followed by trifluoroacetylation with ethyl trifluoroacetate to give the required intermediate **2** with a yield of 62%. Subsequently, the key [3+2] cyclocondensation was investigated, following the procedure described previously for the selective synthesis of 5-trifluoromethylpyrazoles (vide supra). Unfortunately, treatment of compound **2** with hydrazine hydrate in DMSO at 110 °C for 12 h provided compound **1** in only 23% yield (method A, Scheme 3). Attempts to increase the reaction yield by modifying the reaction temperature and reagent amounts were met with little success. The consistently low yield of the desired product prompted us to search for another approach to its preparation. It was reported that 3-(trifluoromethyl)-1H-pyrazoles tautomerized into 5-(trifluoromethyl)-1H-pyrazoles under basic condition.[13] We then speculated that with the $Cu(OAc)_2$-catalyzed [3+2] cyclocondensation protocol for the synthesis of the 3-fluoromethylpyrazole congener **8**, followed by a facile tautomerization, we could achieve compound **1**. In practice, 2.0 mol% $Cu(OAc)_2$ catalyzed the [3+2] cyclocondensation of **2** with hydrazine hydrate and gave compound **1** in excellent yield (94%, method B, Scheme 3), but it did not afford the expected **8**. Currently, it remained uncertain that the formation of compound **1** was directly resulted from the $Cu(OAc)_2$ catalyzed-[3+2] cyclocondensation or through rapid tautomerization from compound **8**. Efforts to single crystal of compound **1** suitable for X-ray analysis turned out to be fruitless. To verify the regiochemistry of compound **1**, ^{1}H NMR was used as an analytical technique. Compound **1** showed the presence of the C-4 proton of pyrazole at δ = 6.98 ppm which is agreeing with the chemical shift (δ = 7.16-6.97 ppm) of structurally related 3-phenyl-5-trifluoromethyl-1*H*-pyrazoles and well-distinguishable from the signal (δ = 6.82-6.74 ppm) of 5-phenyl-3-trifluoromethyl-1*H*-pyrazoles.[8] With the key intermediate in hand, we then attempted to introduce a methyl group at the 1-position of the pyrazole ring for the synthesis of the penultimate intermediate **9a**. Initial attempts, using general reaction conditions (1.5 equivalents K_2CO_3, 1.5 equivalents CH_3I, DMF, rt), yielded two diasteromeric compounds **9a** and **9b** in a ratio of 3:2. The regiochemistry of **9a** and **9b** was assigned by comparison of their ^{1}H NMR spectrum to those of structurally similar compounds, which were previously reported in the literature. The ^{1}H NMR spectrum of **9a** displayed *N*-methyl signals at δ = 4.09 ppm which is consistent with the chemical shift (δ = 4.03 ppm) of 1-methyl-3-phenyl-5-(trifluoromethyl)-1*H*-pyrazole.[14] In the ^{1}H NMR spectrum of **9b**, a sharp singlet at δ = 3.88 ppm is attributed to *N*-methyl group and consistent with the chemical shift (δ = 3.92 ppm) of 1-methyl-5-phenyl-3-(trifluoromethyl)-1*H*-pyrazole.[15]



Scheme 3 Synthesis of fluazolate via [3+2] cyclocondensation of trifluoromethyl-α,β-ynone **2** with hydrazine hydrate

After a brief survey of the reaction conditions, including reagents, solvents and temperatures, the optimal conditions were established. As shown in Entry 4 of Table 1, compound **1** was treated with Me_2SO_4 in toluene at 80 °C, and the desired compound **9a** was obtained as a major product in 71% yield. Finally, bromination of **9a** with Br_2 in acetic acid gave rise to fluazolate in 85% yield. The spectral data (NMR, IR, and HRMS) of the synthetic fluazolate were found to agree well with those reported previously in the literature.[16]

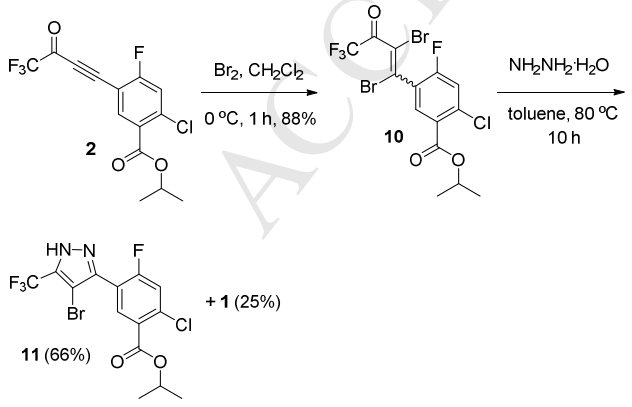
Table 1. Methylation of **1** under various reaction conditions



Entry	Conditions[a]	Yield (%)[b] 9a	9b
1	1.5 equiv MeI, 1.5 equiv K_2CO_3, DMF, rt, 8 h	48%	32%
2	1.5 equiv MeI, 1.5 equiv K_2CO_3, THF, reflux, 6 h	29%	22%
3	1.2 equiv Me_2SO_4, 1.5 equiv K_2CO_3, DMF, reflux, 6 h	32%	30%
4	1.2 equiv Me_2SO_4, toluene, 80 °C, 10 h	71%	15%
5	1.5 equiv Me_2SO_4, 1.5 equiv LiOH, DMF, reflux, 6 h	24%	19%
6	1.2 equiv Me_2SO_4, DMF, 100 °C, 7 h	43%	27%
7	1.5 equiv MeI, 1.5 equiv Na_2CO_3, DMF, rt, 9 h	45%	35%

[a] Substrate **1** (0.28 mmol) and solvent (2 mL)
[b] Isolated yield

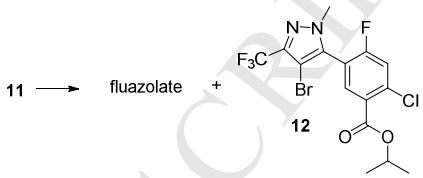
Recently, Nenajdendo et al. reported a nucleophilic substitution-cyclization for the synthesis of 4-bromo-5-(trifluoromethyl)-3-phenyl-1H-pyrazole via the corresponding trifluoromethyl-α,β-dibromoenone.[17] In light of the above results, we turned our attention to an alternative route to fluazolate. We assumed that the 4-bromo-5-(trifluoromethyl)-1H-pyrazole, the core structure of fluazolate, could be assembled via Nenajdendo's protocol, with a subsequent regioselective methylation furnishing fluazolate. Therefore, compound **2** was converted to trifluoromethyl-α,β-dibromoenone **10** in 88% yield as an inseparable mixture of geometric isomers with a ratio of ca. 5.6 : 1.[18] This was carried out simply by exposure of **2** to bromine in CH_2Cl_2 at 0 °C. Nucleophilic substitution-cyclization of this trifluoromethyl-α,β-dibromoenone with hydrazine hydrate was then performed in toluene at 80 °C to give compound **11** in 66% yield and compound **1** in 25% yield.[19] Other solvents, such as chlorobenzene, THF, *t*-BuOH and CH_2Cl_2, were examined but gave inferior results in terms of both yield and selectivity.



Scheme 4 Synthesis of compound **11** via nucleophilic substitution-cyclization of compound **10** with hydrazine hydrate

The final step of the secondary synthetic route was to introduce a methyl group. Disappointingly, using the procedure delineated previously for the methylation of compound **1** (vide supra), **11** was methylated and gave fluazolate in 50% yield and the unwanted isomer **12** in 35% yield (Table 2, Entry 1). The low selectivity could be attributed to the higher acidity of the NH proton in compound **11**, which resulted in reduced activation energy barrier for interconversion between the tautomers. After examining several reaction conditions, this problem was finally circumvented by using a silver(I)-mediated methylation process (Table 2, Entry 4). Thus, the reaction of **11** with methyl iodide and silver oxide in acetonitrile at room temperature gave rise to 71% yield of fluazolate and 19% yield of **12**.

Table 2. Methylation of **11** under various reaction conditions



Entry	Conditions[a]	Yield (%)[b] fluazolate	12
1	1.2 equiv Me_2SO_4, toluene, 80 °C, 10 h	50%	35%
2	1.5 equiv MeI, 1.5 equiv K_2CO_3, THF, reflux, 8 h	28%	42%
3	1.5 equiv MeI, 1.5 equiv Na_2CO_3, DMF, reflux, 8 h	25%	50%
4	1.5 equiv MeI, 1.0 equiv Ag_2O, CH_3CN, rt, 3 h	71%	19%
5	1.5 equiv MeI, 1.0 equiv Ag_2CO_3, CH_3CN, rt, 3 h	57%	23%
6	1.5 equiv MeI, 1.0 equiv $AgNO_3$, CH_3CN, rt, 3 h	53%	20%
7	1.5 equiv MeI, 1.0 equiv Ag_2O, CH_3CN, 0 °C, 14 h	54%	15%

[a] Substrate **1** (0.28 mmol) and solvent (2 mL)
[b] Isolated yield

3. Conclusion

In summary, two new routes have been developed that are suitable for the synthesis of fluazolate in up to 30% overall yield. The first strategy, involves a $Cu(OAc)_2$-catalyzed [3+2] cyclocondensation combined with a facile tautomerization and a regioselective methylation of the resulting adduct, as efficient key steps in the creation of target compound. This synthetic endeavor further demonstrates and reinforces the generality of our [3+2] cyclocondensation to the synthesis of 5-trifluoromethylpyrazole-based bioactive compounds. The second strategy, which applied a nucleophilic substitution-cyclization protocol and a silver (I)-mediated methylation process as key steps, was also successful in constructing fluazolate. It is believed that the work reported in this paper will be a valuable addition to both academic research and industrial application.

4. Experimental section

4.1. General procedure

All reactions were performed under an atmosphere of air unless otherwise stated. All solvents and reagents were employed as received. Analytical thin layer chromatography was performed on SiO_2 60 F-254 plates and flash column chromatography was

carried out using SiO_2 60 (particle size 0.040-0.055 mm, 230–400 mesh), both of which are available from E. Merck. Visualization was performed under UV irradiation at 254 nm followed by staining with aqueous potassium permanganate ($KMnO_4$ (3 g) and K_2CO_3 (20 g) in 300 mL of H_2O containing 5 mL of an aqueous solution of NaOH (5%, w/v)) and charring by heat gun. Fourier transform infrared spectra (IR) were recorded on Shimadzu spectrum IRPrestige-21 system and expressed in cm^{-1}. ^1H , ^{19}F and ^{13}C NMR spectra were recorded on Bruker 500 FT NMR. Chloroform-d and Methanol-d were used as the solvent and TMS (δ = 0.00 ppm) as an internal standard. Chemical shifts are reported as δ values in ppm as referenced to TMS. Multiplicities are recorded as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sext (sextet), sept (septet), dd (doublet of doublets), dt (doublet of triplets), br (broad), m (multiplet). Coupling constants (J) are expressed in Hz. HRMS were measured by JEOL JMS-HX110 spectrometer and spectral data were recorded as m/z values. Melting points were measured using an Electrothermal instrument.

4.2 2-Chloro-4-fluoro-5-iodobenzoic acid (3)

A mixture of 2-chloro-4-fluorobenzoic acid **4** (4.000 g, 22.91 mmol), $NaIO_3$ (0.906 g, 4.58 mmol) and I_2 (2.037 g, 8.02 mmol) in conc. H_2SO_4 (40 mL) was stirred at room temperature for 8 hours. Chilled water (100 mL) was added to quench the reaction. The resulting solid was filtered, washed with H_2O, dired at 50 ^oC in vaccum to give the white solid **3** (6.824 g, 99% yield). Mp 124-126 ^oC; IR (neat): 1700, 1580, 1558, 1400, 1348, 1298, 1258 cm^{-1}; ^1H NMR (500 MHz, CD_3OD): δ = 8.33 (d, *J* = 7.0 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD): δ = 164.9, 163.3 (d, *J* = 250.0 Hz), 142.0 (d, *J* = 3.7 Hz), 135.1 (d, *J* = 10.0 Hz), 128.4, 117.9 (d, *J* = 28.7 Hz), 78.1 (d, *J* = 26.2 Hz); ^{19}F NMR (470 MHz, CD_3OD): δ = -89.5; HRMS (EI) m/z $[M]^+$ calcd. for $C_7H_3ClFIO_2$: 299.8850; found: 299.8855.

4.3 Isopropyl 2-chloro-4-fluoro-5-iodobenzoate (5)

To a stirred solution of compound **3** (2.200 g, 7.33 mmol) in anhydrous DMF (20 mL) was added K_2CO_3 (0.846 g, 8.06 mmol) and isopropyl iodide (1.870 g, 10.99 mmol) in sequence at room temperature. The resulting mixture was stirred at the same temperature for 6 hours and saturated $NH_4Cl_{(aq)}$ (10 mL) was added to quench the reaction. The aqueous layer was separated and extracted with EtOAc (20 x 3 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated to give the crude residue, which was purified by flash chromatography on silical gel with EtOAc/*n*-hexane (1:19) to afford compound **5** (2.407 g, 96% yield) as white solid. Mp 43-44 ^oC; IR (neat): 1732, 1714, 1585, 1558, 1463, 1371, 1284, 1271, 1255 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.23 (d, *J* = 6.5 Hz, 1H), 7.19 (dd, *J* = 7.5, 1.0 Hz, 1H), 5.28 (septet, *J* = 6.0 Hz, 1H), 1.41 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.1, 163.0 (d, *J* = 252.5 Hz), 141.9 (d, *J* = 2.5 Hz), 135.5 (d, *J* = 10.0 Hz), 128.4 (d, *J* = 3.7 Hz), 118.4 (d, *J* = 26.2 Hz), 78.6 (d, *J* = 26.2 Hz), 69.9, 21.8 (2xCH_3); ^{19}F NMR (470 MHz, $CDCl_3$): δ = -89.5; HRMS (EI) m/z $[M]^+$ calcd. for $C_{10}H_9ClFIO_2$: 341.9320; found: 341.9321.

4.4 Isopropyl 2-chloro-4-fluoro-5-((trimethylsilyl)ethynyl) benzoate (6)

A mixture of **5** (1.700 g, 4.96 mmol), CuI (47 mg, 0.25 mmol), $Pd(PPh_3)_4$ (138 mg, 0.12 mmol) was stirred in THF (35 mL) at room temperature. The resulting mixture was degassed by bubbling N_2 through it for 10 mins. Then Et_3N (2.000 g, 19.84 mmol) was added thereto and stirred for another 10 mins before addition of trimethylsilyl acetylene (0.540 g, 5.46 mmol). The reaction mixture was stirred at 80 ^oC for 2 hours and H_2O (30 mL) was added to quench the reaction. The aqueous layer was separated and extracted with EtOAc (20 x 3 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated to give the crude residue, which was purified by flash chromatography on silical gel with EtOAc/*n*-hexane (1:29) to afford compound **6** as a white solid (1.458 g, 93%). Mp 38-39 ^oC; IR (neat): 1730, 1714, 1583, 1556, 1463, 1455, 1396, 1346, 1282, 1269, 1255 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 7.5 Hz, 1H), 7.20 (d, *J* = 9.0 Hz, 1H), 5.28 (septet, *J* = 6.0 Hz, 1H), 1.41 (d, *J* = 6.5 Hz, 6H), 0.29 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.6 (d, *J* = 258.7 Hz), 163.6, 136.6 (d, *J* = 2.5 Hz), 135.1 (d, *J* = 10.0 Hz), 126.9 (d, *J* = 3.7 Hz), 118.5 (d, *J* = 23.7 Hz), 110.9 (d, *J* = 16.2 Hz), 102.4 (d, *J* = 2.5 Hz), 95.7, 69.7, 21.8 (2xCH_3), -0.92 (3xCH_3); ^{19}F NMR (470 MHz, $CDCl_3$): δ = -103.1; HRMS (EI) m/z $[M]^+$ calcd. for $C_{15}H_{18}ClFO_2Si$: 312.0749; found: 312.0745.

4.5 Isopropyl 2-chloro-5-ethynyl-4-fluorobenzoate (7)

To a stirred solution of **6** (1.400 g, 4.49 mmol) in anhydrous THF (15 mL) was added TBAF (1 M in THF, 5.84 mL, 5.84 mmol) in small portions at 0^oC. The resulting mixture was stirred at the same temperature for 0.5 hour and then saturated $NH_4Cl_{(aq)}$ (10 mL) was added to quench the reaction. The aqueous layer was separated and extracted with EtOAc (15 x 3 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated to give the crude residue, which was purified by flash chromatography on silical gel with EtOAc/*n*-hexane (1:19) to afford compound **7** as a white solid (1.032 g, 96%). Mp 34-35 ^oC; IR (neat): 1732, 1710, 1606, 1562, 1481, 1386, 1294, 1273, 1103 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 7.5 Hz, 1H), 7.23 (d, *J* = 9.0 Hz, 1H), 5.27 (septet, *J* = 6.0 Hz, 1H), 3.40 (s, 1H), 1.40 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.9 (d, *J* = 260.0 Hz), 163.5, 136.9 (d, *J* = 2.5 Hz), 135.8 (d, *J* = 11.2 Hz), 127.0 (d, *J* = 3.7 Hz), 118.6 (d, *J* = 23.7 Hz), 109.8 (d, *J* = 16.2 Hz), 84.1 (d, *J* = 3.7 Hz), 75.1, 69.8, 21.8 (2xCH_3); ^{19}F NMR (470 MHz, $CDCl_3$): δ = -103.1; HRMS (EI) m/z $[M]^+$ calcd. for $C_{12}H_{10}ClFO_2$: 240.0353; found: 240.0355.

4.5 Isopropyl 2-chloro-4-fluoro-5-(4,4,4-trifluoro-3-oxobut-1-yn-1-yl)benzoate (2)

To a stirred solution of **7** (0.560 g, 2.34 mmol) in anhydrous THF (20 mL) was added *n*-BuLi (2.21 mL, 1.6M, 3.50 mmol) dropwise at -60 ^oC. The resulting solution was stirred at the same temperature for 30 min, at which time a solution of ethyl trifluoromethylacetate (0.365 g, 2.56 mmol) and $BF_3{\cdot}OEt_2$ (0.331 g, 2.34 mmol) in anhydrous THF (8 mL) was introduced dropwise. After reaction was complete (ca. 1h), water (8 mL) and saturated NH_4Cl solution (6 mL) was added. The aqueous layer was separated and extracted with EA (2 x 25 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated to give the crude product, which was purified by flash chromatography on silica gel with EtOAc/*n*-hexane (1:9) to afford compound **2** (0.485 g, 62%) as white solid. Mp 61-63 ^oC; IR (neat): 1730, 1712, 1606, 1568, 1556, 1485, 1392, 1294 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 9.0 Hz, 1H), 7.35 (d, *J* = 8.5 Hz, 1H), 5.30 (septet, *J* = 6.5 Hz, 1H), 1.42 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.8 (q, *J* = 43.7 Hz), 164.5 (d, *J* = 265.0 Hz), 162.7, 140.3 (d, *J* = 11.2 Hz), 138.0, 128.0 (d, *J* = 3.7 Hz), 119.4 (d, *J* = 23.7 Hz), 114.7 (q, *J* = 285.0 Hz), 106.2 (d, *J* = 16.2 Hz), 90.6, 88.0, 70.4, 21.7 (2xCH_3); ^{19}F NMR (470 MHz, $CDCl_3$): δ = -77.8, -99.5;

HRMS (EI) m/z $[M]^+$ calcd. for $C_{14}H_9ClF_4O_3$: 336.0176; found: 336.0177.

4.6 Isopropyl 2-chloro-4-fluoro-5-(5-(trifluoromethyl)-1H-pyrazol-3-yl)benzoate (1)

To a stirred solution of compound **2** (0.220 g, 0.65 mmol) and $Cu(OAc)_2$ (3 mg, 0.016 mmol) in CH_2Cl_2 (4 mL) was added hydrazine hydrate (39 mg, 0.65 mmol). The resulting mixture was stirred under reflux for 2 hour. Then saturated NH_4Cl solution (2 mL) was added to quench the reaction. The aqueous layer was separated and extracted with CH_2Cl_2 (2 x 4 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated to give the crude residue, which was purified by flash chromatography on silical gel with EtOAc/*n*-hexane (1:5) to afford compound **1** (0.212 g, 94% yield) as white solid. Mp 56-57 ^oC; IR (neat): 1733, 1714, 1616, 1581, 1456, 1378, 1274, 1178 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.18 (d, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 10.5 Hz, 1H), 6.98 (s, 1H), 5.31 (septet, *J* = 6.5 Hz, 1H), 1.41 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.9, 159.8 (d, *J* = 256.2 Hz), 137.9, 135.7 (d, *J* = 11.2 Hz), 130.9 (d, *J* = 5.0 Hz), 128.0 ((d, *J* = 2.5 Hz), 120.9 (q, *J* = 267.5 Hz), 119.5 (d, *J* = 25.0 Hz), 115.2 (d, *J* = 12.5 Hz), 103.6, 70.3, 21.7 (2xCH_3); ^{19}F NMR (470 MHz, $CDCl_3$): δ = -62.2, -109.6; HRMS (EI) m/z $[M]^+$ calcd. for $C_{14}H_{11}ClF_4N_2O_2$: 350.0445; found: 350.0439

4.7 Isopropyl 2-chloro-4-fluoro-5-(1-methyl-5-(trifluoromethyl) -1H-pyrazol-3-yl)benzoate (9a) and isopropyl 2-chloro-4-fluoro-5-(1-methyl-3-(trifluoromethyl) -1H-pyrazol-5-yl)benzoate (9b)

A solution of **1** (104 mg, 0.30 mmol) and Me_2SO_4 (45 mg, 0.36 mmol) in toluene (3 mL) was stirred at room temperature for 10 h. The reaction was then quenched with water and the aqueous layer was separated and extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated to give the crude product, which was purified by flash chromatography on silica gel with EtOAc/*n*-hexane (1:9) to afford compound **9a** (77 mg, 71%) and **9b** (16 mg, 15%).

9a White solid; mp 78-80 ^oC; IR (neat): 1732, 1716, 1617, 1578, 1454, 1380, 1270, 1173 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.48 (d, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 11.0 Hz, 1H), 7.05 (s, 1H), 5.31 (septet, *J* = 6.0 Hz, 1H), 4.09 (s, 3H), 1.42 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.6, 160.5 (d, *J* = 243.5 Hz), 142.1, 141.8, 137.0 (d, *J* = 7.5 Hz), 134.4, 127.8, 119.3 (d, *J* = 25.0 Hz), 118.7 (q, *J* = 273.7 Hz), 116.1 (d, *J* = 15.0 Hz), 106.2, 70.1, 38.0, 21.8 (2xCH_3); ^{19}F NMR (470 MHz, $CDCl_3$): δ = -62.1, -106.1; HRMS (EI) m/z $[M]^+$ calcd. for $C_{15}H_{13}ClF_4N_2O_2$: 364.0602; found: 364.0605.

9b White solid; mp 93-94 ^oC; IR (neat): 1730, 1716, 1616, 1574, 1454, 1375, 1274, 1174 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.88 (d, *J* = 8.0 Hz, 1H), 7.39 (d, *J* = 9.0 Hz, 1H), 6.66 (s, 1H), 5.31 (septet, *J* = 6.0 Hz, 1H), 3.88 (s, 3H), 1.42 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.3, 160.5 (d, *J* = 256.2 Hz), 143.1, 134.2 (d, *J* = 10.0 Hz), 131.1 (d, *J* = 3.7 Hz), 127.5 ((d, *J* = 3.7 Hz), 119.8 (q, *J* = 266.2 Hz), 119.0 (d, *J* = 22.5 Hz), 107.9 (d, *J* = 10.0 Hz), 69.6, 29.7, 21.8 (2xCH_3); ^{19}F NMR (470 MHz, $CDCl_3$): δ = -60.5, -109.8; HRMS (EI) m/z $[M]^+$ calcd. for $C_{15}H_{13}ClF_4N_2O_2$: 364.0602; found: 364.0600.

4.8 (E) and (Z)-isopropyl-2-chloro-5-(1,2-dibromo-4,4,4-trifluoro-3-oxobut-1-en-1-yl)-4-fluorobenozoate (10)

A mixture of **2** (170 mg, 0.50 mmol) and Br_2 (120 mg, 0.75 mmol) in CH_2Cl_2 (6 mL) was stirred at 0 ^oC for 1 hour. The volatiles were removed in vacuo and the resulting mixture was purified by flash chromatography on silica gel with EtOAc/*n*-hexane (1:9) to afford compound **10** (cis + trans mixture, 220 mg, 88% yield) as yellow oil. IR (neat): 1653, 1583, 1560, 1490, 1272, 1188, 1140 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.90-7.88 (m, 1H), 7.33 (d, *J* = 9.0 Hz, 0.14H), 7.24 (d, *J* = 9.5 Hz, 0.86H), 5.28 (septet, *J* = 6.5 Hz, 1H), 1.44-1.40 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) major isomer: δ = 177.8 (q, *J* = 40.0 Hz), 163.1, 158.6 (d, *J* = 258.7 Hz), 138.1, 133.8, 130.3, 127.5, 124.0, 119.4, 118.4, 114.9 (q, *J* = 288.7 Hz), 70.4, 21.7 (2xCH_3). ^{19}F NMR (470 MHz, $CDCl_3$) major isomer: δ = -72.3, -104.5. minor isomer: δ = -72.8, -106.8; HRMS (EI) m/z $[M]^+$ calcd. for $C_{14}H_9Br_2ClF_4O_3$: 493.8543; found: 493.8535.

4.9 Isopropyl-5-(4-bromo-5-(trifluoromethyl)-1H-pyrazol-3-yl)-2-chloro-4-fluoro- benzoate (11)

A mixture of **10** (102 mg, 0.20 mmol) and hydrazine hydrate (13 mg, 0.26 mmol) in toluene (3 mL) was stirred at 80 ^oC for 10 hours. The volatiles were removed in vacuo and the resulting mixture was purified by flash chromatography on silica gel with EtOAc/*n*-hexane (1:9) to afford compound **1** (22 mg, 25% yield) and **11** (58 mg, 66% yield) as white solid.Compound **11** Mp 61-62 ^oC; IR (neat): 1730, 1715, 1615, 1571, 1454, 1376, 1272, 1178 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.40 (d, *J* = 7.5 Hz, 1H), 7.39 (d, *J* = 10.0 Hz, 1H), 5.30 (septet, *J* = 6.0 Hz, 1H), 1.41 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.6, 160.2 (d, *J* = 257.5 Hz), 141.9, 137.2 (d, *J* = 10.0 Hz), 135.9, 133.3 (d, *J* = 3.7 Hz), 127.7 ((d, *J* = 2.5 Hz), 121.7, 119.4 (d, *J* = 26.2 Hz), 113.8 (d, *J* = 13.7 Hz), 92.5, 70.2, 21.8 (2xCH_3); ^{19}F NMR (470 MHz, $CDCl_3$): δ = -62.2, -107.5; HRMS (EI) m/z $[M]^+$ calcd. for $C_{14}H_{10}BrClF_4N_2O_2$: 427.9550; found: 427.9555.

4.10 Fluazolate and Isopropyl-5-(4-bromo-1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)-2-chloro-4-fluorobenzoate (12)

A mixture of **11** (121 mg, 0.28 mmol), Ag_2O (63 mg, 0.28 mmol) and MeI (61 mg, 0.42 mmol) in CH_3CN (3 mL) was stirred at room temperature for 3 h. The reaction was then quenched with water and the aqueous layer was separated and extracted with EtOAc (2x3 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated to give the crude product, which was purified by flash chromatography on silica gel with EtOAc/*n*-hexane (1:9) to afford **fluazolate** (100 mg, 71%) as white solid and **12** (24 mg, 19%) as white solid.

Fluazolate Mp 81-83 ^oC; IR (neat): 1732, 1714, 1618, 1571, 1537, 1454, 1375, 1267, 1178, 1145, 1130 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 8.5 Hz, 1H), 5.30 (septet, *J* = 6.5 Hz, 1H), 4.12 (s, 3H), 1.41 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.8, 161.0 (d, *J* = 258.7 Hz), 144.3, 136.3 (d, *J* = 10.0 Hz), 134.8 (d, *J* = 3.7 Hz), 130.6 (q, *J* = 38.7 Hz), 127.0 (d, *J* = 3.7 Hz), 119.5 (q, *J* = 267.5 Hz), 119.1 (d, *J* = 25.0 Hz), 117.8 (d, *J* = 15.0 Hz), 96.2, 69.6, 40.1, 21.8 (2xCH_3); ^{19}F NMR (470 MHz, $CDCl_3$): δ = -58.7, -105.4; HRMS (EI) m/z $[M]^+$ calcd. for $C_{15}H_{12}BrClF_4N_2O_2$: 441.9707; found: 441.9700.

Compound **12** Mp 61-63 ^oC; IR (neat): 1732, 1714, 1618, 1574, 1454, 1377, 1274, 1170, 1143, 1103 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 7.5 Hz, 1H), 7.43 (d, *J* = 9.0 Hz, 1H), 5.13 (septet, *J* = 6.0 Hz, 1H), 3.86 (s, 3H), 1.42 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.4, 160.7 (d, *J* = 257.5 Hz), 140.1 (q, *J* = 37.5 Hz), 138.0 (d, *J* = 10.0 Hz), 136.7, 135.2, 127.7 ((d, *J* = 3.7 Hz), 120.4 (q, *J* = 267.5 Hz), 119.5 (d, *J* = 25 Hz), 114.8 (d, *J* = 8.7 Hz), 93.6, 70.2, 38.9, 21.7 (2xCH_3); ^{19}F NMR (470 MHz, $CDCl_3$): δ = -62.3, -105.1; HRMS (EI) m/z $[M]^+$ calcd. for $C_{15}H_{12}BrClF_4N_2O_2$: 441.9707; found: 441.9702.

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References

1. (a) Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, S; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen , A. W.; Zhang, Y. Y.; Isakson, P. C. *J. Med. Chem.* **1997**, *40*, 1347-1365; (b) Kaur, K.; Kumar, V.; Gupta, G. K. *J. fluorine Chem.* **2015**, *178*, 306-326.
2. (a) Lee, E.; Choi, M. K.; Youk, H. J.; Kim, C. H.; Han, I. C.; Yoo, B. C.; Lee, M. K.; Lim, S. J. *J. Cancer Res. Clin. Oncol.* **2006**, *132*, 223-233; (b) Brenneis, C.; Maier, T. J.; Schmidt, R.; Hofacker, A.; Zulauf, L.; Jakobsson, P. J.; Scholich, K.; Geisslinger, G. *FASEB J.* **2006**, *20*, 1352-1360.
3. Sun, A.; Chandrakumar, N.; Yoon, J.-J.; Plemper, R. K.; Snyder, J. P. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5199-5203.
4. Wong, P. C.; Crain, E. J.; Watson, C. A.; Wexler, R. R.; Lam, P. Y.; Quan, M. L.; Knabb, R. M. *J. Thromb. Thrombolysis* **2007**, *24*, 43-51.
5. Lahm, G. P.; Selby, T. P.; Freudenberger, J. H.; Stevenson, T. M.; Myers, B. J.; Seburyamo, G.; Smith, B. K.; Flexner, L.; Clark, C. E.; Cordova, D. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4898-4906.
6. Hamper, B. C.; Mao, M. K.; Phillips, W. G. US 6121458 A.
7. For recent articles: (a) Zora, M.; Kivrak, A.; Yazici, C. *J. Org. Chem.* **2011**, *76*, 6726-6742; (b) Janin, Y. L. *Chem. Rev.* **2012**, *112*, 3924-3958; (c) Fustero, S.; Sánchez-Roselló, M.; Barrio, P.; Simón-Fuentes, A. *Chem. Rev.* **2011**, *111*, 6984-7034; (d) Li, F.; Nie, J.; Sun, L.; Zheng, Y.; Ma, J.-A. *Angew. Chem. Int. Ed.* **2013**, *52*, 6255-6258. *Angew. Chem.* **2013**, *125*, 6375-6378; (e) Mykhailiuk, P. K. *Chem. Eur. J.* **2014**, *20*, 1-7; (f) Iminov, R. T.; Mashkov, A. V.; Vyzir, I. I.; Chalyk, B. A.; Tverdokhlebov, A. V.; Mykhailiuk, P. K.; Babichenko, L. N.; Tolmachev, A. A.; Volovenko, Y. M.; Biitseva, A.; Shishkin, O. V.; Shishkina, S. V. *Eur. J. Org.* Chem. **2015**, 4, 886-891; (g) Rulev, A. Y.; Romanov, A. R. RSC Adv. **2016**, 6, 1984-1988; (h) Vincent-Rocan, J.-F.; Ivanovich, R. A.; Clavette, C.; Leckett, K.; Bejjani, J.; Beauchemin, A. M. Chem. Sci. **2016**, 7, 315-328; (i) Sloop, J. C.; Holder, C.; Henary, M. Eur. J. Org. Chem. **2015**, 16, 3405-3422; (j) Wen, J. J.; Ding, C.-K.; Ding, Z.-C.; Li, T.; Zhan, Z.-P. Eur. J. Org. Chem. **2015**, 23, 5230-5235.
8. Hsieh, M.-T.; Kuo, S.-C.; Lin, H.-C. *Adv. Synth. Catal.* **2015**, *357*, 683-689.
9. Maxwell, B. D. *J. Labelled. Cpd. Radiopharm.* **2000**, *43*, 645-654.
10. Foster, R. S.; Jakobi, H.; Harrity, J. P. A. *Org. Lett.* **2012**, *14*, 4858-4861.
11. For the synthesis of 1,1,1-trifluoro-4-(trimethylstannyl)but-3-yn-2-one, refer to: Koldobskii, A. B.; Tsvetkov, N .P.; Verteletskii, P. V.; Godovikov, I. A.; Kalinin, V. N. *Russ. Chem. Bull. Int. Ed.* **2009**, *58*, 1431-1437.
12. (a) Zhang, W.; Moore, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 12796; (b) Tai, C.-L.; Hung, M.-S.; Pawar, V.-D.; Tseng, S.-L.; Song, J.-S.; Hsieh, W.-P.; Chiu, H.-H.; Wu, H.-C.; Hsieh, M.-T.; Kuo, C.-W.; Hsieh, C.-C.; Tsao, J.-P.; Chao, Y.-S.; Shia, K.-S. *Org. Biomol. Chem.* **2008**, *6*, 447-450.
13. (a) Corbett, J. W.; Elliott, R. L.; Bell, A. S. WO 2008065508 A1; (b) Day, R. F.; Lafontaine, J. A. US 200252392 A1.
14. Dai, J. J.; Fang, C.; Xiao, B.; Yi, J.; Xu, J.; Liu, Z.-J.; Lu, X.; Liu, L.; Fu, Y. *J. Am. Soc. Chem.* **2013**, *135*, 8436-8439.
15. Dvorak, C. A.; Rudolph, D. A.; Ma, S.; Carruthers, N. I. *J. Org. Chem.* **2005**, *70*, 4188-4190.
16. Rouchaud, J.; Neus, O.; Cools, K.; *Bulcke*, R. *Bull. Environ. Contam. Toxicol.* **2000**, *64*, 651-658.
17. Muzalevskiy, V. M.; Iskandarov, A. A.; Nenajdenko, V. G. *Mendeleev Commun.* **2014**, *24*, 342-344.
18. The ratio of isomers was determined by the relative intensity of the aromatic proton signals in the ^{1}H NMR spectrum.
19. Compound **10** could be converted into **2** through a halophilic reaction mechanism[17] followed by [3+2] cyclocondensation to give compound **1**.