Fluorine-Sacrificial Cyclizations as an Access to 5-Fluoropyrazoles

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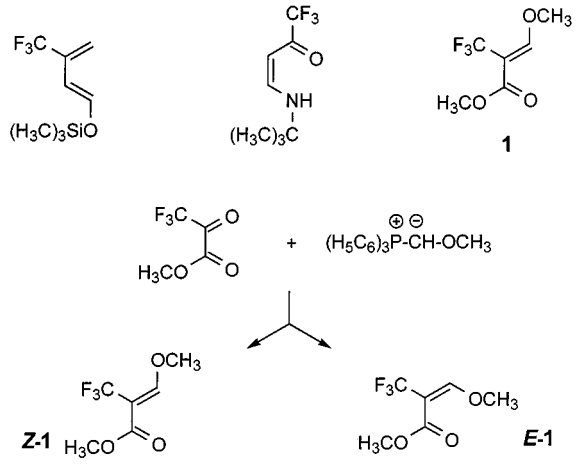
Methyl 3-methoxy-2-trifluoromethylacrylate **1**, readily prepared by Wittig reaction from methyl 3,3,3-trifluoropyruvate, has been treated with a number of aryl- (or hetaryl-) hydrazines. Under mild base-catalysis, the resulting 3-hydrazinoacrylates **6** undergo consecutive hydrogen fluoride elimination and intramolecular nucleophilic addition to afford methyl 1-(het)aryl-5-fluoropyrazole-4-carboxylates **7**. 5-Aminopyrazoles **8** have been obtained by direct reaction of the ester **7a** with a lithium amide, whereas 5-fluoro-1-phenylpyrazole-4-carboxamides **10** have been formed by condensation of the 5-fluoro-1-phenylpyrazole-4-carboxylic acid **9** with amines.

Introduction

Previously, this laboratory has devoted considerable effort towards the preparation of ''fluoroisoprene'' (2-fluoro-3-methyl-1,3-butadiene)[1–3] and its homologues,[2–5] including congeners bearing electron-withdrawing[2,6] and electron-donating[6–9] heterofunctional groups, as well as 2-fluoro-2-alkenals[10] and the corresponding *N*-*tert*-butyl imines[11] and *N*,*N*-dimethylhydrazones.[12] These fluorinated building blocks have been employed as versatile modules in chain-lengthening (“fluoroisoprenylation”)[11] or Diels–Alder cycloaddition[2,4,7,8,12] reactions. More recently, the acyl chloride and the methyl ester of 2-fluoro-3-methoxyacrylic acid have been used as electrophilic components in Knorr–Effenberger type and other cyclization reactions, allowing access to a host of fluorine-bearing pyrazolones, uracils, 2-quinolones, 2-chromenones (2*H*-1-benzopyran-2-ones), 1-thio-2-chromenones, and benzothiazepinones.[9,13,14]

We decided to prepare methyl 3-methoxy-2-trifluoromethyl-2-propenoate (**1**) in order to extend the latter studies towards the assembly of trifluoromethyl-substituted heterocycles. We had hitherto gained access to this class of compounds through the use of two other building blocks, namely 3-trifluoromethyl-1-trimethylsilyloxy-1,3-butadiene[15] and 4-*tert*-butylamino-1,1,1-trifluoro-3-buten-2-one,[16,17] a synthetic equivalent of 4,4,4-trifluoro-3-oxobutanal.

The required key intermediate **1** was readily obtained by a Wittig reaction between methyl 3,3,3-trifluoropyruvate (methyl 3,3,3-trifluoro-2-oxopropanoate)[18,19] and (triphenylphosphonio)methoxymethanide.[20,21] The product was isolated as a 2:3 (*Z*/*E*) mixture and was used as such in all subsequent reactions.



Upon gentle warming, ester **1** underwent a condensation reaction with aniline to afford (*E*)-methyl 3-anilino-2-trifluoromethyl-2-propenoate (**2a**; 92%). Heating this intermediate to 100 °C in the presence of polyphosphoric acid gave 4-quinolone as the sole identifiable product (**3a**; 24%). Apparently, repeated 1,4-dehydrofluorination followed by addition of water led to a transformation of the trifluoromethyl substituent into a carboxy function and then the latter was lost in a typical β-oxo-assisted decarboxylation process. With *N*-methylaniline, the reaction sequence took a slightly different course. (N-Methylanilido)acrylate (**2b**; 52%), derived from this amine as a 1:4 (*Z*/*E*) mixture, was converted into methyl 1-methyl-4-quinolone-3-carboxylate (**3b**; 44%) as the major cyclization product. Lastly, methyl 3-(2-aminophenyl)amino-2-trifluoromethyl-2-propenoate (**4**; 89%) and methyl 1*H*-4-isopropyloxy-1,5-benzodiazepine-3-carboxylate (**5b**; 7%) were obtained when 1,2-phenylenediamine was employed as the starting material.

Fluoride elimination/nucleophile addition sequences are responsible for the lability of 2- and 4-(trifluoromethyl)-phenol under basic conditions.[22,23] Similar transformations of trifluoromethyl groups by two-step nucleophilic substitutions have been reported for 4-(trifluoromethyl)ani-

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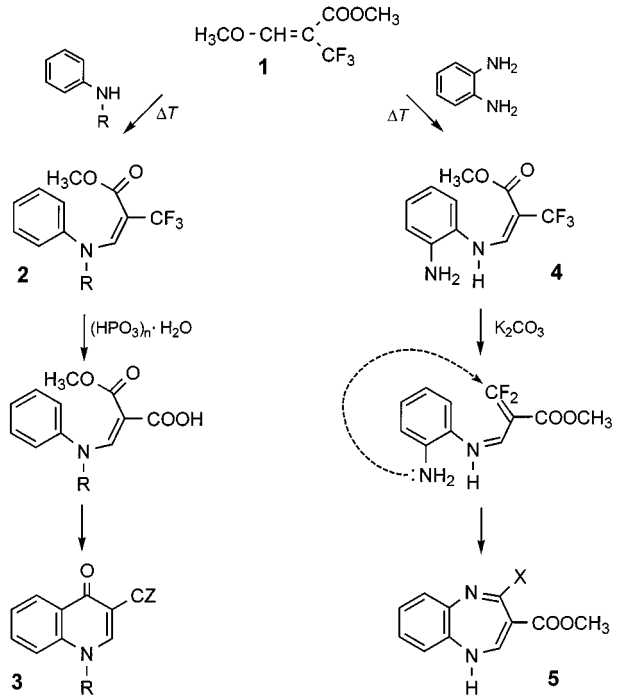
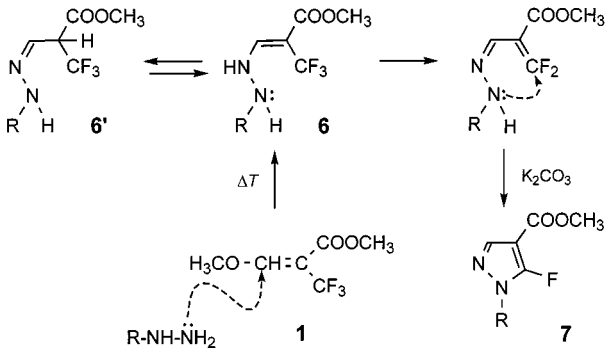


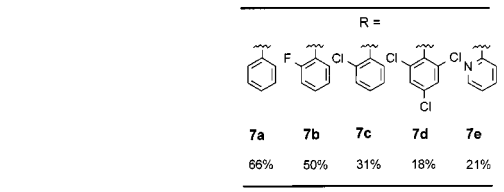
cpd.	R	CZ	yield
3a	R	H	22%
3b	CH_3	$COOCH_3$	23%

cpd.	X	yield
5a	F	-
5b	$OCH(CH_3)_2$	6%

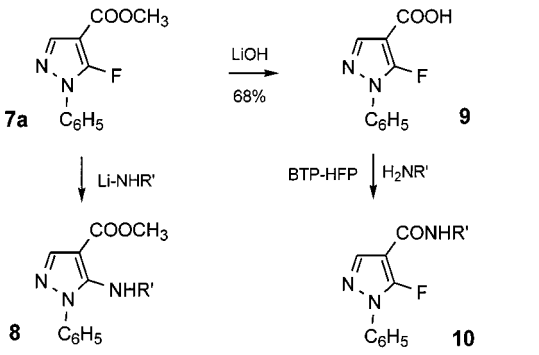
line,[24,25] 4-(nonofluorobutyl)aniline,[26] 2- and 3-(trifluoromethyl)indole,[27,28] and 5-amino-2-chloro-4-(trifluoromethyl)thiazole.[29] The irreversible inhibition of decarboxylases, transaminases, and racemases by a variety of β-fluoroamines also involves the elimination of hydrogen fluoride and subsequent binding to the enzyme through a cysteine residue.[30] 1-(2-Hydroxyphenyl)-2,3,3,3-tetrafluoropropanone[31,32] and *N*-(2-hydroxyphenyl)-2,2,2-trifluoro-1-(trifluoromethyl)ethylamine[33] undergo base-promoted dehydrofluorination followed by intramolecular nucleophilic attack of the phenolate oxygen to afford a 2-substituted 3-fluoro-4*H*-1-benzopyran-4-one (a chromenone) and 2-fluoro-3-trifluoromethyl-1,4-benzoxazine, respectively. *N*-Alkylidene-2-(trifluoromethyl)anilines react with nucleophiles such as butyllithium, lithium diisopropylamide, or potassium *tert*-butoxide to afford quinolines bearing the nucleophile moiety at the 4-position.[34–37] 4-Fluoroquinolines can be prepared by trapping of (6-difluoromethylene-2,4-cyclohexadienylidene)amine, generated from 2-(trifluoromethyl)aniline, with nucleophiles such as acetylides, enolates, or eneimides (α-deprotonated aliphatic nitriles).[26,38] Other methods involving dehydrofluorination and cyclization through intramolecular nucleophilic addition lead to 1,2-dihydro-3-trifluoromethyl-4-pyridazinones,[39] to 2-fluoroindoles, -benzofurans, and -benzothiophenes,[40] and to 3-trifluoromethyl- (or 3-perfluoroalkyl-), 4-fluoro-, or both 3-trifluoromethyl- and 4-fluoro-substituted pyrazoles.[41–43]

It became apparent that methyl 3-methoxy-2-(trifluoromethyl)acrylate (**1**) described above offers a convenient access to 5-fluoropyrazole derivatives. When the ester **1** was heated in the presence of an aryl- (or hetaryl)- hydrazine, smooth replacement of the methoxy group occurred. The methyl 3-(het)arylhydrazino-2-(trifluoromethyl)acrylates **6** thus formed were found to exist in equilibrium with the tautomeric species **6'**. Fluorine-sacrificial cyclization occurred under weakly basic conditions, a first elimination of hydrogen fluoride initiating intramolecular addition of the terminal nitrogen atom to the halogen-bearing carbon, and a second one, as the last stage of the ring-closure process, affording methyl 1-(het)aryl-5-fluoropyrazole-4-carboxylates **7** as the final products.





7a	**7b**	**7c**	**7d**	**7e**
66%	50%	31%	18%	21%



cpd.	R'	yield
8a	C_6H_5	84%
8b	*p*-C_6H_4-OCH_3	74%

cpd.	R'	yield
10a	C_6H_5	41%
10b	*o*-C_6H_4-OCH_3	37%
10c	*m*-C_6H_4-OCH_3	42%
10d	*p*-C_6H_4-OCH_3	58%

When solutions of ester **7a** and lithium anilide or lithium *p*-anisidide in tetrahydrofuran were mixed, the methyl 5-amino-1-phenylpyrazole-4-carboxylates **8a** (84%) and **8b** (74%) were rapidly formed in a nucleophilic 1,4-addition/fluoride elimination sequence. Alternatively, ester **7a** could

be saponified to give the carboxylic acid **9**, and the latter could then be converted into the carboxamides **10** by condensation with various aromatic amines in the presence of (1-benzotriazolyloxy)tripyrrolidinophosphonium hexafluorophosphate (BTP-HFP).[44]

The new access to 5-fluoropyrazoles **7** reported herein has its limitations. We were unable to isolate any heterocyclic compounds following attempted reactions between acrylate **1** and *alkyl*hydrazines. We are currently focussing on acylhydrazines and hydroxylamines as potential cyclization components.

Experimental Section

General Remarks: For standard operations and abbreviations, refer to recent publications from this laboratory.[45,46] ^{1}H- and ^{19}F NMR spectra were recorded in deuteriochloroform solution at 400 and 376 MHz, respectively. Mass spectra were obtained after chemical ionization (CI) and only ^{35}Cl isotopomers are listed in the case of chlorinated compounds.

Preparation of the Key Starting Material: Methyl 3-Methoxy-2-trifluoromethyl-2-propenoate (1): (Methoxymethyl)triphenylphosphonium bromide (58 g, 0.15 mol) was added to a solution of *tert*-butyllithium (0.15 mol) in a 2:1 mixture (250 mL) of tetrahydrofuran and pentane cooled to –75 °C. After stirring vigorously for 15 min at –25 °C, the mixture was cooled to –75 °C once more, whereupon methyl trifluoropyruvate[18,19] (23 g, 0.15 mol) was added. The reaction mixture was allowed to warm to 25 °C and then poured into cold (–25 °C) pentane (250 mL). After the addition of diatomaceous earth (kieselguhr), the solid material was removed by suction filtration and the filtrate was concentrated. On distillation under reduced pressure, a colorless liquid was collected; 14.1 g (51%); b.p. 79–81 °C/5 Torr. – $C_6H_7F_3O_3$ (184.11): calcd. C 39.14, H 3.83; found C 39.31, H 3.93.

On the basis of gas chromatographic (30 m, DB-1701, 100 °C; 30 m, DB-FFAP, 100 °C) and NMR analyses, the product was found to consist of the (*Z*) and (*E*) isomers in a 2:3 ratio. – ^{1}H NMR of *Z*-**1**: δ = 7.24 (q, *J* = 1.5, 1 H), 4.02 (s, 3 H), 3.80 (s, 3 H). – ^{1}H NMR of *E*-**1**: δ = 7.62 (s, 1 H), 4.01 (s, 3 H), 3.78 (s, 3 H). – ^{19}F NMR of *Z*-**1**: δ = –61.8 (d, *J* = 1.5 Hz). – ^{19}F NMR of *E*-**1**: δ = –58.8 (s). – MS (CI, GC-coupled) of *Z*-**1**: *m*/*z* (%) = 202 (46) [M^+ + NH_4], 185 (83) [M^+ + 1], 184 (16) [M^+], 153 (100). – MS (CI, GC-coupled) of *E*-**1**: *m*/*z* (%) = 202 (63) [M^+ + NH_4], 185 (35) [M^+ + 1], 184 (20) [M^+], 153 (100).

3-Amino-2-(trifluoromethyl)acrylates and Cyclization Products Derived Therefrom: Methyl 3-Anilino-2-trifluoromethyl-2-propenoate (2a): A mixture of methyl 3-methoxy-2-trifluoromethyl-2-propenoate **1** (5.5 g, 30 mmol) and aniline (2.7 mL, 2.8 g, 30 mmol) was heated at 100 °C for 1 h. The product was then absorbed on silica and eluted with a 1:20 mixture (*v*/*v*) of ethyl acetate and hexanes. Upon recrystallization of the white solid from hexanes, colorless needles were obtained; m.p. 68–70 °C; 6.8 g (92%). – ^{1}H NMR: δ = 10.47 (br. d, *J* = 13.3 Hz, 1 H), 7.85 (d, *J* = 13.3 Hz, 1 H), 7.36 (t, *J* = 7.9 Hz, 2 H), 7.14 (t, *J* = 7.9 Hz, 1 H), 7.06 (d, *J* = 7.9 Hz, 2 H), 3.84 (s, 3 H). – ^{19}F NMR: δ = –60.0 (s). – MS (CI): *m*/*z* (%) = 263 (33) [M^+ + NH_4], 246 (100) [M^+ + 1], 245 (20) [M^+], 226 (90). – $C_{11}H_{10}F_3NO_2$ (245.20): calcd. C 53.88, H 4.11; found C 53.73, H 4.15.

Methyl 3-Methylanilino-2-trifluoromethyl-2-propenoate (2b): The above procedure was repeated by using *N*-methylaniline (3.3 mL, 3.2 g, 30 mmol) instead of aniline and heating at 100 °C was prolonged to 5 h. The corresponding substitution product, isolated by column chromatography, was found to exist as a 1:4 (*Z*/*E*) mixture; b.p. 98–99 °C/0.8 Torr; 4.0 g (52%). – ^{1}H NMR of *Z*-**2b**: δ = 7.97 (q, *J* = 1.5 Hz, 1 H), 7.4 (m, 5 H), 3.76 (s, 3 H), 3.46 (q, *J* = 3.0 Hz, 3 H). – ^{1}H NMR of *E*-**2**: δ = 7.3 (m, 6 H), 3.69 (s, 3 H), 3.38 (s, 3 H). – ^{19}F NMR of *Z*-**2b**: δ = –51.3 (s). – ^{19}F NMR of *E*-**2b**: δ = –59.0 (s). – $C_{12}H_{12}F_3NO_2$ (259.23): calcd. C 55.60, H 4.66; found C 55.61, H 4.75.

Methyl 3-(2-Aminoanilino)-2-trifluoromethyl-2-propenoate (4): A similar reaction as above was performed with 1,2-phenylenediamine (3.2 g, 30 mmol), but this substrate was dissolved together with the acrylate **1** in methanol (100 mL) and the resulting solution was heated under reflux for 2 h. After evaporation of the solvent, the crude product was purified by chromatography on silica, again by using a 1:20 (*v*/*v*) mixture of ethyl acetate and hexanes as eluent; m.p. 113–115 °C (from hexanes); 6.9 g (89%). – ^{1}H NMR: δ = 10.24 (br. d, *J* = 13.0 Hz, 1 H), 7.73 (dd, *J* = 13.0, 1.0 Hz, 1 H), 7.0 (m, 2 H), 6.85 (td, *J* = 7.5, 1.0 Hz, 1 H), 6.81 (dd, *J* = 8.0, 1.0 Hz, 1 H), 3.84 (s, 3 H), 3.63 (br. s, 2 H). – ^{19}F NMR: δ = –60.2 (d, *J* = 1.0 Hz). – MS (CI): *m*/*z* (%) = 278 (12) [M^+ + NH_4], 261 (100) [M^+ + 1], 260 (22) [M^+], 241 (35), 119 (49). – $C_{11}H_{11}F_3N_2O_2$ (260.21): calcd. C 50.77, H 4.26; found C 50.98, H 3.89.

4*H*-4-Quinolinone (3a): The 3-aminoacrylate **2a** (2.5 g, 10 mmol) was added to polyphosphoric acid (15 mL) and the mixture was heated at 100 °C for 1 h. Neutralization, extraction, and subsequent chromatography (see above) afforded 4-quinolinone (4-hydroxyquinoline) as a white solid; m.p. and mixed m.p. 194–197 °C (ref.[47] 196–197 °C); 0.35 g (24%; 22% based on **1**).

Methyl 1,4-Dihydro-1-methyl-4-oxoquinoline-3-carboxylate (3b): Analogous treatment of aminoacrylate **2b** (10 mmol) afforded the ester **3b**; m.p. 189–191 °C (after sublimation; ref.[48] 185–186 °C); 0.50 g (44%; 23% based on **1**). – ^{1}H NMR: δ = 8.51 (dd, *J* = 8.0, 1.5 Hz, 1 H), 8.46 (s, 1 H), 7.70 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1 H), 7.4 (m, 2 H), 3.92 (s, 3 H), 3.88 (s, 3 H). – MS (CI): *m*/*z* (%) = 218 (100) [M^+ + 1], 217 (18) [M^+], 186 (35), 159 (55).

Methyl 4-Isopropyloxy-1*H*-1,5-benzodiazepine-3-carboxylate (5b): The aminoacrylate **4** (10 mmol) was added to a suspension of potassium carbonate (2.8 g, 20 mmol) in propan-2-ol (100 mL). The mixture was heated under reflux for 45 min, the solvent was then evaporated, and the product was isolated by chromatography; m.p. 170–171 °C (after sublimation); 0.18 g (7%; 6% based on **1**). – ^{1}H NMR: δ = 7.47 (d, *J* = 8.0 Hz, 1 H), 7.0 (m, 1 H), 6.88 (dd, *J* = 8.0, 1.5 Hz, 1 H), 6.82 (td, *J* = 8.0, 1.5 Hz, 1 H), 6.36 (dd, *J* = 8.0, 1.5 Hz, 1 H), 5.38 (br. d, *J* = 8.0 Hz, 1 H), 5.24 (sept, *J* = 6.3 Hz, 1 H), 3.69 (s, 3 H), 1.31 (d, *J* = 6.3 Hz, 6 H). – MS (CI): *m*/*z* (%) = 261 (79) [M^+ + 1], 260 (47) [M^+], 219 (50), 186 (49), 119 (100). – $C_{14}H_{16}N_2O_3$ (260.29): calcd. C 64.60, H 6.20; found C 65.19, H 5.66.

3-*N*'-(Het)Arylhydrazino-2-(trifluoromethyl)acrylates and Cyclization Products Derived Therefrom: Methyl 3-*N*'-Phenylhydrazino-2-trifluoromethyl-2-propenoate (6a): A mixture of the acrylate **1** (7.4 g, 40 mmol) and phenylhydrazine (3.9 mL, 4.3 g, 40 mmol) was heated under reflux for 2 h. A 2:1 mixture of the 3-hydrazinoacrylate **6a** and the 3-hydrazonopropionate **6a'** was obtained; 8.6 g (83%) after purification by chromatography on silica. – ^{1}H NMR: δ = 9.45 (br. d, *J* = 10.9 Hz, 0.7 H), 7.79 (s, 0.3 H), 7.54 (d, *J* = 10.9 Hz, 0.7 H), 7.26 (t, *J* = 7.9 Hz, 2 H), 7.0 (m, 1.6 H), 6.89 (t, *J* = 7.4 Hz, 0.3 H), 6.78 (d, *J* = 7.9 Hz, 1.4 H), 6.09 (br. s, 0.7 H), 4.13 (qd, *J* = 8.5, 1.0 Hz, 0.3 H), 3.80 (s, 0.9 H), 3.78 (s, 2.1 H).

When the tautomeric mixture was triturated with pentanes, the pure hydrazino derivative **6a** crystallized; 39%; m.p. 97–99 °C (after sublimation). – ^{19}F NMR: δ = –60.3 (s). – MS (CI): *m*/*z* (%) = 278 (22) [$M^+ + NH_4$], 261 (94) [$M^+ + 1$], 260 (10) [M^+], 241 (23), 94 (100). – $C_{11}H_{11}F_3N_2O_2$ (260.21): calcd. C 50.77, H 4.26; found C 50.91, H 4.20.

Methyl 3-*N*'-(2-Fluorophenyl)hydrazino-2-trifluoromethyl-2-propenoate (6b): Analogously formed as a 3:2 hydrazino/hydrazono mixture (**6b/6b'**) by using 2-fluorophenylhydrazine[49,50] (5.0 g, 40 mmol) in the above procedure; 9.1 g (82%) after purification by chromatography on silica. – ^{1}H NMR: δ = 9.42 (br. d, *J* = 10.9 Hz, 0.6 H), 7.97 (br. s, 0.4 H), 7.55 (d, *J* = 10.9 Hz, 0.6 H), 7.41 (td, *J* = 8.5, 1.5 Hz, 0.4 H), 7.11 (d, *J* = 7.0 Hz, 0.4 H), 7.0 (m, 2 H), 6.9 (m, 1.2 H), 6.8 (m, 0.4 H), 6.40 (br. s, 0.6 H), 4.14 (qd, *J* = 8.5, 1.0 Hz, 0.4 H), 3.82 (s, 1.2 H), 3.79 (s, 1.8 H). – The pure hydrazino tautomer **6b** (30%) crystallized from the mixture of **6b** and **6b'** upon trituration with pentanes; m.p. 102–104 °C (after sublimation). – ^{19}F NMR: δ = –60.5 (s, 3 F), –134.8 (m, 1 F). – MS (CI): *m*/*z* (%) = 296 (4) [$M^+ + NH_4$], 279 (42) [$M^+ + 1$], 278 (19) [M^+], 112 (100). – $C_{11}H_{10}F_4N_4O_2$ (278.20): calcd. C 47.49, H 3.62; found C 47.29, H 3.66.

Methyl 3-*N*'-(2-Chlorophenyl)hydrazino-2-trifluoromethyl-2-propenoate (6c): Use of 2-chlorophenylhydrazine[50,51] (5.7 g, 40 mmol) in the above procedure again afforded a 3:2 hydrazino/hydrazono mixture (**6c/6c'**); 9.4 g (80%) after purification by chromatography on silica. – ^{1}H NMR: δ = 9.46 (br. d, *J* = 10.9 Hz, 0.6 H), 8.21 (br. s, 0.4 H), 7.55 (d, *J* = 11.0 Hz, 0.6 H), 7.44 (dd, *J* = 8.5, 1.5 Hz, 0.4 H), 7.31 (dd, *J* = 7.8, 1.5 Hz, 0.6 H), 7.25 (td, *J* = 7.6, 1.5 Hz, 0.6 H), 7.22 (d, *J* = 7.6 Hz, 0.8 H), 7.16 (d, *J* = 7.3 Hz, 0.4 H), 6.9 (m, 1.2 H), 6.82 (td, *J* = 7.6, 1.5 Hz, 0.4 H), 6.61 (br. s, 0.6 H), 4.15 (qd, *J* = 8.5, 1.0 Hz, 0.4 H), 3.83 (s, 1.2 H), 3.81 (s, 1.8 H). – The pure, crystalline hydrazino tautomer **6c** (27%) was isolated upon trituration of the tautomeric mixture of **6c** and **6c'** with pentanes; m.p. 97–99 °C (after sublimation). – ^{19}F NMR: δ = –60.5 (s). – MS (CI): *m*/*z* (%) = 314 (6), 312 (15) [$M^+ + NH_4$], 297 (33), 296 (16), 295 (100) [$M^+ + 1$], 294 (9) [M^+]. – $C_{11}H_{10}F_3N_2O_2$ (294.66): calcd. C 44.84, H 3.42; found C 44.51, H 3.33.

Methyl 3-*N*'-(2,4,6-Trichlorophenyl)hydrazino-2-trifluoromethyl-2-propenoate (6d): Use of 2,4,6-trichlorophenylhydrazine (8.5 g, 40 mmol) in the above procedure gave a 9:1 hydrazino/hydrazono mixture (**6d/6d'**); 13.1 g (90%) after extraction and drying. – ^{1}H NMR: δ = 9.43 (br. d, *J* = 10.9 Hz, 0.9 H), 7.70 (d, *J* = 10.9 Hz, 0.9 H), 7.59 (br. s, 0.1 H), 7.35 (s, 2.0 H), 6.46 (br. s, 0.9 H), 4.09 (quint., *J* = 8.2 Hz, 0.1 H), 3.82 (s, 0.3 H), 3.76 (br. s, 2.7 H). – The hydrazino tautomer **6d** (77%) was obtained in a pure state by precipitation from a concentrated methanol solution by adding pentanes and subsequent recrystallization from methanol; m.p. 146–150 °C. – ^{19}F NMR: δ = –60.4 (s). – MS (CI): *m*/*z* (%) = 368 (7), 367 (30), 366 (25), 365 (93), 364 (55), 363 (100) [$M^+ + 1$], 362 (37) [M^+]. – $C_{11}H_8Cl_3F_3N_2O_2$ (363.55): calcd. C 36.34, H 2.22; found C 36.37, H 2.10.

Exposure of solutions of the pure hydrazino tautomers **6** to trace amounts of triethylamine led to rapid re-establishment of the hydrazino/hydrazono equilibria. The **6/6'** proportions thus obtained were identical with those initially found (2:1, 3:2, 3:2, and 9:1 in the case of compounds **6a**, **6b**, **6c**, and **6d**, respectively).

Methyl 5-Fluoro-1-phenyl-1*H*-pyrazole-4-carboxylate (7a): Potassium carbonate (2.8 g, 20 mmol) was added to a solution of the hydrazino/hydrazono derivative **6a/6a'** in propan-2-ol (200 mL). The mixture was heated under reflux for 45 min and then concentrated to dryness. The residue was purified by chromatography on silica by using a 1:9 (*v*/*v*) mixture of ethyl acetate and hexanes as eluent; 3.5 g (79%). An additional sublimation was required to obtain the product in a colorless state; m.p. 82–83 °C. – ^{1}H NMR: δ = 7.96 (d, *J* = 2.5 Hz, 1 H), 7.64 (dd, *J* = 7.9, 1.3 Hz, 2 H), 7.51 (t, *J* = 7.9 Hz, 2 H), 7.41 (t, *J* = 7.9 Hz, 1 H), 3.88 (s, 3 H). – ^{19}F NMR: δ = –123.3 (m). – MS (CI): *m*/*z* (%) = 238 (5) [$M^+ + NH_4$], 221 (100) [$M^+ + 1$], 220 (37) [M^+], 189 (26). – $C_{11}H_9FN_2O_2$ (220.20): calcd. C 60.00, H 4.12; found C 59.94, H 4.19.

Methyl 5-Fluoro-1-(2-fluorophenyl)-1*H*-pyrazole-4-carboxylate (7b): Prepared analogously from the hydrazino/hydrazono compound **6b/6b'** (5.6 g, 20 mmol); m.p. 75–77 °C (after sublimation); 2.9 g (61%). – ^{1}H NMR: δ = 8.01 (d, *J* = 2.5 Hz, 1 H), 7.54 (td, *J* = 7.6, 1.5 Hz, 1 H), 7.5 (m, 1 H), 7.3 (m, 2 H), 3.88 (s, 3 H). – ^{19}F NMR: δ = –121.9 (dd, *J* = 22.0, 2.5 Hz), –122.3 (m). – MS (CI): *m*/*z* (%) = 256 (7) [$M^+ + NH_4$], 239 (100) [$M^+ + 1$], 238 (12) [M^+], 207 (10). – $C_{11}H_8F_2N_2O_2$ (238.19): calcd. C 55.47, H 3.39; found C 55.39, H 3.16.

Methyl 5-Fluoro-1-(2-chlorophenyl)-1*H*-pyrazole-4-carboxylate (7c): Prepared analogously from the hydrazino/hydrazono compound **6c/6c'** (5.9 g, 20 mmol); m.p. 64–65 °C (after sublimation); 2.0 g (39%). – ^{1}H NMR: δ = 8.01 (d, *J* = 2.5 Hz, 1 H), 7.6 (m, 1 H), 7.5 (m, 3 H), 3.88 (s, 3 H). – ^{19}F NMR: δ = –121.3 (t, *J* = 2.5 Hz). – MS (CI): *m*/*z* (%) = 257 (33), 256 (22), 255 (100) [$M^+ + 1$], 254 (31) [M^+], 223 (47), 225 (17). – $C_{11}H_8ClFN_2O_2$ (254.65): calcd. C 51.88, H 3.17; found C 51.97, H 3.17.

Methyl 5-Fluoro-1-(2,4,6-trichlorophenyl)-1*H*-pyrazole-4-carboxylate (7d): Prepared analogously from the hydrazino/hydrazono compound **6d/6d'** (7.3 g, 20 mmol); m.p. 86–88 °C (after sublimation); 1.3 g (20%). – ^{1}H NMR: δ = 8.06 (d, *J* = 2.4 Hz, 1 H), 7.53 (s, 2 H), 3.89 (s, 3 H). – ^{19}F NMR: δ = –122.1 (d, *J* = 2.4 Hz). – MS (CI): *m*/*z* (%) = 328 (5), 327 (32), 326 (20), 325 (100), 324 (43), 323 (93), 322 (34) [M^+]. – $C_{11}H_6Cl_3FN_2O_2$ (323.54): calcd. C 40.84, H 1.87; found C 40.90, H 2.17.

Methyl 5-Fluoro-1-(2-pyridyl)-1*H*-pyrazole-4-carboxylate (7e): In contrast to the four examples given above, the pyrazole **7e** was prepared without isolating and purifying the corresponding hydrazino/hydrazono intermediate **6e**. Thus, the acrylate **1** (3.7 g, 20 mmol), 2-pyridylhydrazine[52] (2.2 g, 20 mmol), and pyridine (4.9 mL, 4.8 g, 60 mmol) were dissolved in propan-2-ol (200 mL), the mixture was heated under reflux for 2 h, and then concentrated to dryness. The residue was purified by chromatography on silica by using an ethyl acetate/hexanes mixture (1:3, *v*/*v*) as eluent; m.p. 96–98 °C (after sublimation); 0.95 g (21%). – ^{1}H NMR: δ = 8.57 (dd, *J* = 4.8, 1.8 Hz, 1 H), 7.97 (d, *J* = 2.5 Hz, 1 H), 7.89 (ddd, *J* = 8.2, 7.6, 1.8 Hz, 1 H), 7.76 (dd, *J* = 8.2, 0.9 Hz, 1 H), 7.34 (ddd, *J* = 7.6, 4.8, 0.9 Hz, 1 H), 3.89 (s, 3 H). – ^{19}F NMR: δ = –118.8 (d, *J* = 2.5 Hz). – MS (CI): *m*/*z* (%) = 222 (100) [$M^+ + 1$], 221 (8) [M^+], 190 (18). – $C_{10}H_8FN_3O_2$ (221.19): calcd. C 54.30, H 3.65; found C 54.48, H 3.71.

Methyl 5-Anilino-1-phenyl-1*H*-pyrazole-4-carboxylate (8a): At 0 °C, butyllithium (10 mmol) in hexanes (7 mL) followed by methyl 5-fluoro-1-phenyl-1*H*-pyrazole-3-carboxylate (**7a**; 1.10 g, 5.0 mmol) were added to a solution of aniline (0.91 mL, 0.93 g, 10 mmol) in tetrahydrofuran (15 mL). After 1 h at 25 °C, the mixture was neutralized with ethereal hydrogen chloride, then concentrated and absorbed on silica. Elution with an ethyl acetate/hexanes mixture (1:7, *v*/*v*) afforded product **8a** as colorless needles; m.p. 74–75 °C; 1.2 g (84%). – ^{1}H NMR: δ = 7.97 (s, 1 H), 7.82 (br. s, 1 H), 7.45 (d, *J* = 7.9 Hz, 2 H), 7.19 (t, *J* = 7.9 Hz, 2 H), 7.11 (t, *J* = 7.9 Hz, 1 H), 6.99 (t, *J* = 7.9 Hz, 2 H), 6.81 (t, *J* = 7.9 Hz, 1 H), 6.68 (d, *J* = 7.9 Hz, 2 H), 3.85 (s, 3 H). – MS (CI): *m*/*z* (%) = 294 (100) [$M^+ + 1$], 293 (20) [M^+], 261 (48). – $C_{17}H_{15}N_3O_2$ (293.32): calcd. C 69.61, H 5.15; found C 69.74, H 4.97.

Methyl 5-*p*-Anisidino-1-phenyl-1*H*-pyrazole-4-carboxylate (8b): Analogously, by using *p*-anisidine, product **8b** was prepared and isolated; m.p. 94–96 °C; 1.2 g (74%). – ^{1}H NMR: δ = 7.93 (s, 1 H), 7.84 (br. s, 1 H), 7.36 (d, *J* = 7.4 Hz, 2 H), 7.16 (t, *J* = 7.4 Hz, 2 H), 7.10 (t, *J* = 7.4 Hz, 1 H), 6.65 (d, *J* = 9.0 Hz, 2 H), 6.52 (d, *J* = 9.0 Hz, 2 H), 3.86 (s, 3 H), 3.65 (s, 3 H). – MS (CI): *m*/*z* (%) = 324 (100) [M^+ + 1], 323 (25) [M^+], 291 (33). – $C_{18}H_{17}N_3O_2$ (323.35): calcd. C 66.86, H 5.30; found C 67.05, H 5.00.

5-Fluoro-1-phenyl-1*H*-pyrazole-4-carboxylic Acid (9): The ester **7a** (4.4 g, 20 mmol) was dissolved in a 3:1 (*v*/*v*) mixture (200 mL) of tetrahydrofuran and water and lithium hydroxide monohydrate (0.84 g, 20 mmol) was added portionwise. The solution was kept at 25 °C for 2 h and then acidified with 2 M hydrochloric acid to pH 1. The thick white precipitate thus formed was collected by filtration, dried, and crystallized in the form of tiny needles from a mixture of ethyl acetate and hexanes; m.p. 166–167 °C; 2.8 g (68%). – ^{1}H NMR: δ = 8.02 (d, *J* = 2.5 Hz, 1 H), 7.65 (d, *J* = 7.9 Hz, 2 H), 7.53 (t, *J* = 7.9 Hz, 2 H), 7.43 (t, *J* = 7.9 Hz, 1 H). – ^{19}F NMR: δ = –121.6 (m). – MS (CI): *m*/*z* (%) = 224 (3) [M^+ + NH_4], 207 (100) [M^+ + 1], 206 (46) [M^+]. – $C_{10}H_7FN_2O_2$ (206.18): calcd. C 58.26, H 3.42; found C 57.99, H 3.42.

5-Fluoro-*N*-1-diphenyl-1*H*-pyrazole-4-carboxamide (10a): (1-Benzotriazolyloxy)tripyrrolidinophosphonium hexafluorophosphate[44] (2.6 g, 5.0 mmol), aniline hydrochloride (0.71 g, 5.5 mmol), and diisopropylethylamine (2.1 mL, 1.6 g, 13 mmol) were successively added to a solution of the 5-fluoropyrazole acid **9** (1.0 g, 5.0 mmol) in dichloromethane (25 mL). The resulting heterogeneous mixture was stirred for 2 h at 25 °C, then the solvent was evaporated and the crude product was purified by chromatography on silica by using a 1:4 (*v*/*v*) mixture of ethyl acetate and hexanes as eluent; m.p. 153–155 °C (from hexanes); 0.58 g (41%). – ^{1}H NMR: δ = 8.06 (d, *J* = 2.7 Hz, 1 H), 7.7 (m, 2 H), 7.60 (d, *J* = 7.4 Hz, 2 H), 7.54 (br. s, 1 H), 7.53 (t, *J* = 7.9 Hz, 2 H), 7.43 (t, *J* = 7.4 Hz, 1 H), 7.37 (t, *J* = 7.9 Hz, 2 H), 7.15 (t, *J* = 7.4 Hz, 1 H). – ^{19}F NMR: δ = –127.3 (br. s). – MS (CI): *m*/*z* (%) = 299 (5) [M^+ + NH_4], 282 (100) [M^+ + 1], 281 (15) [M^+], 189 (16). – $C_{16}H_{12}FN_3O$ (281.29): calcd. C 68.32, H 4.30; found C 68.35, H 4.20.

5-Fluoro-*N*-2-methoxyphenyl-1-phenyl-1*H*-pyrazole-4-carboxamide (10b): Prepared analogously as described above by using *o*-anisidine hydrochloride (0.88 g, 5.5 mmol) instead of aniline hydrochloride; m.p. 109–111 °C (from ethyl acetate/hexanes); 0.57 g (37%). – ^{1}H NMR: δ = 8.47 (dd, *J* = 7.9, 1.5 Hz, 1 H), 8.30 (br. s, 1 H), 8.06 (d, *J* = 3.0 Hz, 1 H), 7.7 (m, 2 H), 7.53 (t, *J* = 7.9 Hz, 2 H), 7.43 (t, *J* = 7.9 Hz, 1 H), 7.08 (td, *J* = 7.9, 1.5 Hz, 1 H), 7.00 (td, *J* = 7.9, 1.5 Hz, 1 H), 6.91 (dd, *J* = 7.9, 1.5 Hz, 1 H), 3.93 (s, 3 H). – ^{19}F NMR: δ = –127.5 (br. s). – MS (CI): *m*/*z* (%) = 312 (100) [M^+ + 1], 311 (15) [M^+], 189 (16). – $C_{17}H_{14}FNO_2$ (311.31): calcd. C 65.59, H 4.53; found C 65.58, H 4.69.

5-Fluoro-*N*-3-methoxyphenyl-1-phenyl-1*H*-pyrazole-4-carboxamide (10c): Prepared analogously as described above by using *m*-anisidine hydrochloride (0.88 g, 5.5 mmol) instead of aniline hydrochloride; m.p. 120–122 °C (from ethyl acetate/hexanes); 0.65 g (42%). – ^{1}H NMR: δ = 8.05 (d, *J* = 2.7 Hz, 1 H), 7.7 (m, 2 H), 7.5 (m, 3 H), 7.43 (tt, *J* = 7.4, 1.2 Hz, 1 H), 7.39 (t, *J* = 2.4 Hz, 1 H), 7.25 (t, *J* = 4.1 Hz, 1 H), 7.04 (ddd, *J* = 8.2, 1.8, 0.9 Hz, 1 H), 6.71 (ddd, *J* = 8.2, 2.4, 0.9 Hz, 1 H), 3.82 (s, 3 H). – ^{19}F NMR: δ = –127.3 (br. s). – MS (CI): *m*/*z* (%) = 329 (3) [M^+ + NH_4], 312 (100) [M^+ + 1], 311 (23) [M^+], 189 (15). – $C_{17}H_{14}FN_3O_2$ (311.31): calcd. C 65.59, H 4.53; found C 66.01, H 4.74.

5-Fluoro-*N*-4-methoxyphenyl-1-phenyl-1*H*-pyrazole-4-carboxamide (10d): Prepared analogously as described above by using *p*-anisidine hydrochloride (0.88 g, 5.5 mmol) instead of aniline hydrochloride; m.p. 163–165 °C (from ethyl acetate/hexanes); 0.90 g (58%). – ^{1}H NMR: δ = 8.04 (br. s, 1 H), 7.66 (dd, *J* = 7.9, 1.5 Hz, 2 H), 7.5 (m, 4 H), 7.4 (m, 2 H), 6.9 (m, 2 H), 3.81 (s, 3 H). – ^{19}F NMR: δ = –127.5 (br. s). – MS (CI): *m*/*z* (%) = 329 (1) [M^+ + NH_4], 312 (100) [M^+ + 1], 311 (23) [M^+], 189 (15). – $C_{17}H_{14}FN_3O_2$ (311.32): calcd. C 65.59, H 4.53; found C 65.22, H 4.53.

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