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Synthesis of 3-Amino-4-fluoropyrazoles

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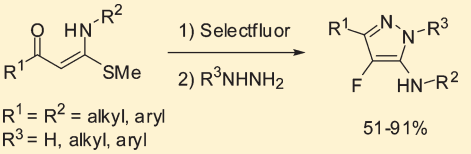
Supporting Information

ABSTRACT: Fluorinated pyrazoles bearing additional functional groups that allow further functionalization are of considerable interest as building blocks in medicinal chemistry. The developed synthetic strategy for new 3-amino-4-fluoropyrazoles consists of a monofluorination of β-methylthio-β-enaminoketones using 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor) toward the corresponding monofluorinated enaminoketones, followed by condensation with different hydrazines.



In the search for new bioactive compounds, the introduction of fluorine atoms into organic structures has proven to be a valuable tool for changing the physical and chemical properties of the compound without major steric implications.[1,2] In that respect, there is a growing demand for synthetic methods for the preparation of selectively fluorinated heterocyclic compounds for use in pharmaceutical and agrochemical industry.[3] Pyrazoles, which can be considered as bioisosteres of pyrroles,[4] are widely used as pharmaceuticals and agrochemicals.[5−7] Consequently, fluorinated pyrazoles are of specific interest because the introduction of a fluorine atom can drastically affect the biological properties of members of this class of heterocycles. Unfortunately, in contrast to chlorinated, brominated, or trifluoroalkylated pyrazoles,[8,9] the synthesis of ring-fluorinated pyrazoles has been more problematic and less well studied.[10−14] Fluoropyrazoles have been synthesized via direct electrophilic fluorination of the pyrazole ring, but this strategy generally proceeds with low yields.[10] Cyclocondensation reactions of fluorinated β-dicarbonyl compounds or α,β-unsaturated carbonyl compounds with hydrazines are more generally applicable and give better yields of the corresponding fluoropyrazoles.[11−14] Because of the established activity of the bicyclic aminopyrazoles Zaleplon, Sildenafil, and Allopurinol, there has been a revival of the interest in the particular class of pyrazoles bearing an amino substituent.[15−19] More specifically, 3-amino-4-fluoropyrazoles have been used, albeit to a limited extend, to synthesize bioactive compounds with potential for treating eating disorders,[20] diabetes,[21] and inflammatory diseases.[22] Substituted 3-amino-4-fluoropyrazoles have also been used as gastric acid inhibitors,[23] insecticides, and acaricides.[24] Unfortunately, only limited synthetic pathways for synthesizing 3-amino-4-fluoropyrazoles are available. Some ring-fluorinated 3-aminopyrazoles have been synthesized following a rather inefficient direct fluorination approach using *N*-fluorodibenzenesulfonimide (NFSI),[20] 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor),[21] or trifluoromethylhypofluorite[23] and via the photochemical decomposition of diazonium tetrafluoroborates.[25] 3,5-Diamino-4-fluoropyrazoles were synthesized via reaction of 3-amino-3-chloro-2-fluoroacrylimidoyl chloride and phenylhydrazine.[26] Another strategy makes use of *N*-alkyl imidates prepared from methyl 2-cyano-2-fluoroacetate, in condensation reactions with trichlorophenylhydrazine to give 3-amino-4-fluoro-5-hydroxypyrazoles in low yields.[27] It is clear that no straightforward method for synthesizing functionalized 3-amino-4-fluoropyrazoles is available, although 3-amino-4-fluoropyrazoles make up a class of compounds with considerable potential as building blocks in medicinal chemistry. Recently, an efficient synthesis of 3-amino-4-fluoro-5-phenylpyrazole, via the condensation of benzoylfluoroacetonitrile with hydrazine, has been described.[28] However, the starting benzoylfluoroacetonitrile is not easily prepared because of the problematic selective monofluorination of benzoylacetonitrile. To overcome the undesired difluorination of the starting substrates, other synthetic strategies toward 3-amino-4-fluoropyrazoles have been developed starting from β-methylthio-β-enaminoketones instead of β-ketonitriles.

An important general procedure for the synthesis of 3-aminopyrazoles involves the cyclocondensation of β-methylthio-β-enaminoketones **2** with hydrazines. These substituted β-enaminoketones are useful 1,3-dielectrophiles and have demonstrated their potential in the synthesis of amino-substituted five- and six-member heterocycles.[29,30] Furthermore, the condensation of these *N*,*S*-acetals with unsymmetrical hydrazines such as phenylhydrazine can result in 5-amino-1-arylpyrazoles in a highly regiocontrolled fashion.[31] The use of fluorinated β-methylthio-β-enaminoketones **4** for the synthesis of fluorinated aminopyrazoles offers interesting perspectives. It should be noted that fluorinated β-methylthio-β-enaminoketones have not been

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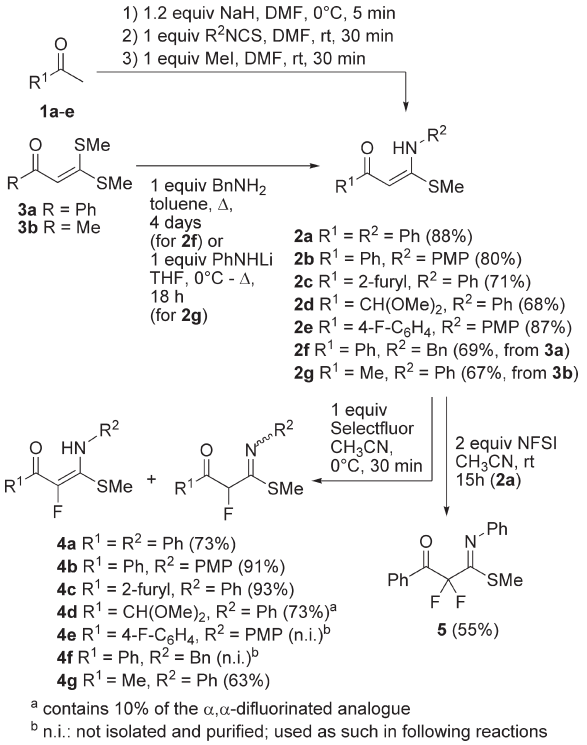
Scheme 1. Synthesis of α-Fluorinated Ketones 4a−g



[a] contains 10% of the α,α-difluorinated analogue
[b] n.i.: not isolated and purified; used as such in following reactions

described so far except for some very specific 2-fluoro-2-(1,3-thiazolylidene)ethanones.[32−34]

3-(Methylthio)-1-phenyl-3-(phenylamino)prop-2-en-1-one **2a** is easily available from acetophenone **1a** via deprotonation with sodium hydride and reaction with phenyl isothiocyanate, followed by quenching with iodomethane (Scheme 1).[35] However, when the same reaction was evaluated using α-fluoroacetophenone, no fluorinated α-oxoketene *N*,*S*-acetal **4a** was formed, most probably because of the reduced nucleophilicity of the fluorinated enolate derived from fluoroacetophenone. Also, the enamine derived from α-fluoroacetophenone and pyrrolidine[36] did not react with phenyl isothiocyanate to give the desired compound **4a**. In a next attempt to synthesize fluorinated β-methylthio-β-enaminoketones **4**, the electrophilic fluorination of β-enaminoketones **2** was investigated. 3-(Methylthio)-1-phenyl-3-(phenylamino)prop-2-en-1-one **2a** was treated with 1.0 equiv of 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor) in acetonitrile at 0 °C, which nicely resulted in a clean monofluorination toward **4a** within 0.5 h with minor formation of difluorinated product **5** (<5%) (Scheme 1). When using a slight excess of Selectfluor or upon addition of Selectfluor in one portion, an increase of the amount of difluorinated product **5** was observed, which was difficult to separate from the monofluorinated product **4a** via flash chromatography. The fluorination reaction of **2a** toward **4a** using NFSI led to substantial amounts of methyl 2,2-difluoro-3-oxo-*N*,3-diphenylpropanethioimidate **5**, besides the desired monofluorinated compound **4a**. For analytical purposes, the difluorinated reaction product **5** was easily obtained in 55% yield by reaction of **2a** with 2 equiv of NFSI at room temperature. A variety of α-oxoketene *N*,*S*-acetal derivatives **2a**−**g** were synthesized using the procedure described above or via literature procedures (Scheme 1).[37−45] Although some polarized *N*,*S*-ketals are known to occur as tautomeric mixtures of enamine and imine forms,[41] compounds **2a**−**g** were isolated as single enamine isomers. In no case were the methylene protons at C-2 of the β-ketoimidate forms detected by ^{1}H or ^{13}C NMR spectroscopy. The fact that only one geometric form of the enamine was isolated is demonstrated by the sharp signals of the vinylic proton at C-2 and of the thiomethyl moiety in ^{1}H NMR spectra and is in accordance with literature data of related *N*,*S*-ketals.[41] The enamine double bond of compounds **2a**−**g** was shown to adopt an *E* configuration (the thiomethyl and carbonyl groups at opposite sides of the enamine double bond) because of hydrogen bonding of the enamine NH proton with the carbonyl group. This is demonstrated by the significant downfield shift of the NH proton in ^{1}H NMR spectra (recording ^{1}H NMR data using extended X-sweep parameters revealed the presence of broadened signals at 13.2−14.0 ppm) and the presence of stretching vibrations of the NH group at 3000−3300 cm^{-1} and stretching vibrations of the carbonyl groups below 1600 cm^{-1} in infrared spectra. Both IR and ^{1}H NMR data are characteristic of enaminoketones displaying strong internal H-bonds.[35,39,46] Furthermore, NOE experiments showed a strong correlation through space between the vinylic proton at C-2 of **2c** and the SMe moiety (see the Supporting Information), which proves the assigned *E* stereochemistry.

For derivatives **2a**−**e** [R^1 = aryl, R^2 = aryl; or R^2 = Ph, R^1 = $CH(OMe)_2$], the reaction between ketones **1** and aromatic isothiocyanates was performed in the presence of sodium hydride as a base and iodomethane to give α-oxoketene *N*,*S*-acetals **2a**−**e** in good yields. *N*-Benzyl derivative **2f** was prepared in 69% yield from *S*,*S*-acetal **3a** via a described thioacetal exchange reaction using benzylamine.[37] Finally, 4-(methylthio)-4-(phenylamino)but-3-en-2-one **2g** was also prepared by treating 4,4-bis(methylthio)but-3-en-2-one **3b** with aniline in the presence of *n*-BuLi in THF.[38−46]

The selective monofluorination of the prepared β-methylthio-β-enaminoketones **2** toward fluorinated compounds **4** proceeded smoothly with minor formation of difluorinated thioimidates, except for the *N*-benzyl derivative **2f**. In the latter case, the crude reaction mixture after fluorination of **2f** contained starting material, monofluorinated *N*,*S*-acetal **4f**, and difluorinated thioimidate in a ratio of 18:66:16 (calculated via ^{1}H NMR). The obtained compounds were not separated, but the mixture was used directly for further transformations. The ^{1}H and ^{13}C NMR spectra of compounds **4a**−**g** clearly show the presence of an enamine tautomer, as evidenced by the downfield NH shift in ^{1}H NMR, the upfield shift of the enamine SMe group as compared to the imine tautomers, and the presence of a quaternary C-2 in the ^{13}C NMR spectrum (C-2 occurs as a doublet due to coupling with fluorine). Although the enamine tautomers of compounds **4a**−**g** are believed to display a *Z* stereochemistry because of internal hydrogen bonding analogous to the corresponding nonfluorinated oxoketene *N*,*S*-acetals **2a**−**g**, this could not be verified by NOE NMR experiments. It should be noted that the ^{1}H NMR spectra of **4a**−**g** are rather complex because the *N*,*S*-acetals exist as three isomers: the enamino form, the (*E*)-imino form, and the (*Z*)-imino form, which cannot be isolated as single compounds. The imine tautomers of **4a**−**g** clearly exist as mixtures of *E* and *Z* isomers (with respect to the C=N double bond), which is demonstrated by the presence of two vinylic CHF protons and two separated thioimidate SMe groups in both ^{1}H and ^{13}C NMR spectra. It can be postulated that the ^{1}H NMR signals of the vinylic CHF protons of the *Z* isomers of the imine forms of compounds **4a**−**g** show a slightly more upfield shift compared to those of the corresponding *E* isomers, because of

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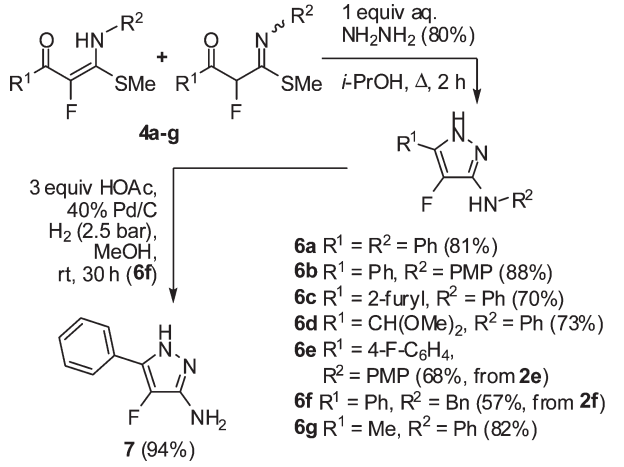
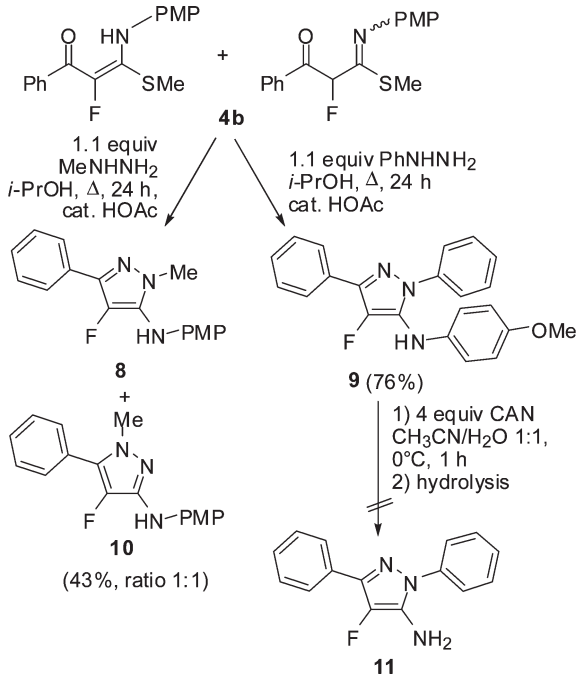
Scheme 2. Synthesis of 3-Amino-4-fluoropyrazoles 6a−g and 7



Scheme 3. Synthesis of 1-Substituted Fluoropyrazoles 8−10



the influence of the free electron pair at the nitrogen atom of the C=N group.[47] Depending on the substitution pattern, the *E*:*Z* isomer ratio of the imine forms of **4a**−**g** ranges from 40:60 to 70:30, while the enamine/imine ratio shifts from 32:68 to 41:59 (calculated from ^{1}H NMR data).

In a next step, the desired 3-amino-4-fluoro-1*H*-pyrazoles **6a**−**g** were efficiently synthesized by heating monofluorinated β-enaminoketones **4a**−**g** and hydrazine hydrate in 2-propanol for 2 h (Scheme 2). The obtained 1*H*-pyrazoles **6a**−**g**, showing a diverse substitution pattern, were easily purified by flash chromatography and recrystallization. To evaluate the possibility of removing the *N*-benzyl protecting group of pyrazole **6f** without losing the fluorine substituent at the pyrazole core, we treated compound **6f** with hydrogen over Pd-C in ethyl acetate in the presence of HOAc. The reaction nicely resulted in 3-amino-4-fluoro-5-phenyl-1*H*-pyrazole **7** in 94% yield. When phenylhydrazine and methylhydrazine were used in the cyclocondensation reaction with compound **4b**, a catalytic amount of acetic acid and prolonged reaction times (24 h) were needed to complete the reaction (Scheme 3). While the reaction of **4b** with phenylhydrazine resulted in only one pyrazole, **9**, the reaction of **4b** with methylhydrazine yielded a 1:1 mixture of 5-amino-1-methylpyrazole **8** and 3-amino-1-methylpyrazole **10**. In an attempt to synthesize 5-amino-1,4-diphenylpyrazole **11**, pyrazole **9** was treated with cerium ammonium nitrate (CAN) in aqueous acetonitrile. Surprisingly, after reaction for 1 h at 0 °C, the intermediate benzoquinone imine appeared to be quite stable toward hydrolysis. Unfortunately, more stringent hydrolytic conditions using 0.5 or 3 M HCl or TFA in dichloromethane, DMF, or acetonitrile all gave rise to complex reaction mixtures and did not lead to the isolation of pyrazole **11**.

In conclusion, it can be stated that a new entry toward 3-amino-4-fluoropyrazoles was developed. These compounds are of considerable interest as building blocks in medicinal chemistry. The developed strategy consists of an efficient chemoselective monofluorination of β-methylthio-β-enaminoketones using Selectfluor toward the corresponding new monofluorinated enaminoketones, followed by condensation with different hydrazines to afford new 3-amino-4-fluoropyrazoles in good yields.

EXPERIMENTAL SECTION

^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz), and ^{19}F NMR (282 MHz) spectra were recorded in $CDCl_3$ unless specified otherwise, using tetramethylsilane (TMS, δ = 0 ppm) as an internal reference for proton spectra. Carbon spectra were referenced to the solvent. ^{19}F NMR spectra were recorded using $CDCl_3$ as a lock solvent. Peak assignments were performed with the use of ^{1}H−^{13}C HSQC 2D-NMR. IR spectra were obtained using an ATR infrared spectrometer. Mass spectra were recorded (70 eV) using either GC−MS coupling or a direct inlet system. LC−MS data were obtained via an electrospray (ES, 4000 V) mass spectrometer. Elemental analysis of new compounds was performed using a CHN elemental analyzer (tin combustion capsules were used for both solids and sticky oils).

(*Z*)-(4-Fluorophenyl)-3-[(4-methoxyphenyl)amino]-3-(methylsulfanyl)prop-2-en-1-one 2e. To an ice-cooled solution of 4.14 g (30 mmol, 1 equiv) of 4′-fluoroacetophenone **1e** in 40 mL of DMF was added 1.44 g (36 mmol, 1.2 equiv) of sodium hydride. Subsequently, a solution of 4.96 g (30 mmol, 1 equiv) of 4-methoxyphenyl isothiocyanate in 20 mL of DMF was added dropwise. The reaction mixture was stirred at room temperature for 45 min. The solution was cooled to 0 °C; 4.26 g (30 mmol, 1 equiv) of iodomethane was added, and the reaction mixture was stirred at room temperature for 45 min. The solution was poured into 100 mL of water (0−5 °C) and extracted with 150 mL of Et_2O. The organic layers were washed with 100 mL of brine and dried over $MgSO_4$. After filtration and evaporation, the residue was purified by chromatography (4:1 hexane/EtOAc; R_f = 0.21) to afford 9.47 g of (4-fluorophenyl)-3-[(4-methoxyphenyl)amino]-3-(methylsulfanyl)prop-2-en-1-one **2e** (26.1 mmol, 88% yield). Analogous compounds **2a**−**d**, **2f**, and **2g** were prepared according to literature procedures.[35−45] **2e**: mp 97−98 °C (1:1 hexane/Et_2O); ^{1}H NMR ($CDCl_3$) δ 2.40 (3H, s, Me), 3.80 (3H, s, Me), 5.78 (1H, s, CH), 6.89 (2H, d, J = 8.8 Hz, 2 × CH), 7.09 (2H, t, J = 8.8 Hz, 2 × CH), 7.22 (2H, d, J = 8.8 Hz, 2 × CH), 7.91 (2H, dd, J = 8.8 Hz, 5.5 Hz, 2 × CH); ^{19}F NMR ($CDCl_3$) δ −109.4 (1F, tt, J = 8.8, 5.5 Hz, CF); ^{13}C NMR ($CDCl_3$) δ 14.5 (Me), 55.3 (Me), 87.3 (CH), 114.1 (2 × CH), 115.1 (d, J = 21.9 Hz, 2 × CH), 127.2 (2 × CH), 129.1 (d, J = 9.2 Hz, 2 × CH), 130.6 (C), 136.4 (C), 158.3 (C), 164.3 (d, J = 250.4 Hz, C), 168.7 (C), 184.3 (C); IR (ATR) ν 3074,

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1596, 1557, 1530 cm^{-1}; MS (ES+) m/z (%) 318 ($M + H^+$, 100). Anal. Calcd for $C_{17}H_{16}FNO_2S$: C, 64.33; H, 5.08; N, 4.41. Found: C, 64.70; H, 5.39; N, 4.55.

Methyl 2,2-Difluoro-3-oxo-*N*,3-diphenylpropanethioimidate 5. To a stirred solution of 2.34 g (7.43 mmol, 2 equiv) of NFSI in 50 mL of acetonitrile under a N_2 atmosphere was added dropwise 1.00 g (3.72 mmol, 1 equiv) of 3-(methylsulfanyl)-1-phenyl-3-(phenylamino)-prop-2-en-1-one **2a** at 0 °C. Stirring was continued for 15 h at room temperature. Subsequently, the mixture was filtered and filtrate was poured into 50 mL of water. The aqueous phase was extracted with 50 mL of diethyl ether and dried over $MgSO_4$. After filtration and evaporation, the oil was purified by silica gel chromatography (4:1 hexane/EtOAc; R_f = 0.43), yielding 0.62 g of methyl 2,2-difluoro-3-oxo-*N*,3-diphenylpropanethioimidate **5** (2.05 mmol, 55% yield) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.60 (3H, s, SCH3), 6.75 (2H, d, J = 7.3 Hz, 2 × CHar), 7.11 (1H, t, J = 7.3 Hz, CHar), 7.29 (2H, d, J = 7.3 Hz, 2 × CHar), 7.49 (2H, d, J = 7.3 Hz, 2 × CHar), 7.61 (1H, tt, J = 7.3, 1.7 Hz, CHar), 8.04 (2H, d, J = 7.3 Hz, 2 × CHar); ^{19}F NMR ($CDCl_3$) δ −98.3 (2F, s, CF_2); ^{13}C NMR ($CDCl_3$) δ 14.0 (SCH_3), 114.4 (t, J = 257.9 Hz, CF_2), 118.8 (2 × CH_{ar}), 125.3 (CH_{ar}), 128.3 (2 × CH_{ar}), 128.7 (2 × CH_{ar}), 129.9 (2 × CH_{ar}), 132.2 (C_{ar}), 133.8 (CH_{ar}), 147.1 (C_{ar}), 159.9 (t, J = 32.9 Hz, C═N), 186.4 (t, J = 27.7 Hz, C═O); IR (ATR) ν 3416, 1711, 1593, 1484 cm^{-1}; MS (ES+) m/z (%) 306 ($M + H^+$, 100).

2-Fluoro-3-(methylsulfanyl)-1-phenyl-3-(phenylamino)-prop-2-en-1-one (enamine, 33%) and Methyl 2-Fluoro-3-oxo-*N*,3-diphenylpropanethioimidate (imines, 67%) 4a. To a solution of 1.00 g (3.72 mmol, 1 equiv) of 3-(methylthio)-1-phenyl-3-(phenylamino)prop-2-en-1-one **2a** in 25 mL of acetonitrile was added in portions 1.31 g (3.72 mmol, 1 equiv) of Selectfluor was under a N_2 atmosphere at 0 °C. The mixture was stirred for 30 min at 0 °C. Subsequently, the reaction mixture was poured into 50 mL of water (0 °C) and 50 mL of dichloromethane. After separation of the organic layer, the aqueous phase was extracted with 2 × 20 mL of dichloromethane. The combined organic phases were dried with $MgSO_4$. Filtration of the drying agents and evaporation of the solvents in vacuo yielded almost pure monofluorinated compound **4a**. Further purification was performed by silica gel chromatography (4:1 hexane/EtOAc; R_f = 0.34) yielding 0.78 g (2.72 mmol, 73% yield) of **4a** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.28 (3H, d, J = 1.7 Hz, SMe), 2.48 (6H, s, 2 × SMe), 6.22 (1H, d, J = 45.1 Hz, CHF), 6.38 (1H, d, J = 46.8 Hz, CHF), 6.74 (2H, s, 2 × CH_{ar}), 6.84 (2H, s, 2 × CH_{ar}), 7.10 (2H, t, J = 7.2 Hz, 2 × CH_{ar}), 7.18 (1H, t, J = 7.2 Hz, CH_{ar}), 7.26−7.39 (8H, m, 8 × CH_{ar}), 7.40−7.53 (7H, m, 7 × CH_{ar}), 7.59 (2H, s, 2 × CH_{ar}), 7.89 (2H, d, J = 7.2 Hz, 2 × CH_{ar}), 8.01−8.17 (4H, m, 4 × CH_{ar}), 11.59 (1H, s, NH); ^{19}F NMR ($CDCl_3$) δ −155.5 (1F, s, CF), −181.5 (1F, d, J = 47.4 Hz, CF), −183.9 (1F, d, J = 47.4 Hz, CF); ^{13}C NMR ($CDCl_3$) δ 12.8 (SMe), 14.2 (SMe), 16.2 (d, J = 8.1 Hz, SMe), 88.2 (d, J = 195.0 Hz, CHF), 94.5 (d, J = 195.0 Hz, CHF), 118.8 (2 × CH_{ar}), 119.8 (2 × CH_{ar}), 123.3 (2 × CH_{ar}), 124.4 (CH_{ar}), 124.7 (CH_{ar}), 125.1 (CH_{ar}), 128.3, 128.5, 128.8, 128.9, 129.0, 129.2, 129.3 (18 × CH_{ar}), 131.7 (CH_{ar}), 134.0 (2 × CH_{ar}), 137.1 (3 × C_{ar}), 139.1 (NC_{ar}), 143.6 (d, J = 225.0 Hz, CF), 148.7 (2 × NC_{ar}), 150.6 (d, J = 27.7 Hz, NCS), 162.2 (2 × C═N), 182.6 (d, J = 25.4 Hz, C═O), 191.4 (2 × C═O); IR (ATR) ν 3347, 3190, 1703, 1595, 1542, 1497, 1487, 1448 cm^{-1}; MS (ES+) m/z (%) 288 ($M + H^+$, 100).

2-Fluoro-3-[(4-methoxyphenyl)amino]-3-(methylsulfanyl)-1-phenylprop-2-en-1-one (enamine, 41%) and Methyl 2-Fluoro-*N*-(4-methoxyphenyl)-3-oxo-3-phenylpropanethioimidate (imines, 59%) 4b. Silica gel chromatography (9:1 hexane/EtOAc; R_f = 0.13) was used: 91% yield; mp 106−107 °C (1:1 hexane/Et_2O); yellow crystals; ^{1}H NMR ($CDCl_3$) δ 2.31 (3H, d, J = 2.2 Hz, SMe), 2.43 (3H, s, SMe), 2.53 (3H, s, SMe), 3.77 [6H, s(broad), 2 × MeO], 3.81 (3H, s, MeO), 6.27 (1H, d, J = 47.4 Hz, CHF), 6.37 (1H, d, J = 48.3 Hz, CHF), 6.73 (2H, d, J = 8.3 Hz, 2 × CH_{ar}), 6.83 (6H, d, J = 8.3 Hz, 6 × CH_{ar}), 6.88 (2H, d, J = 8.3 Hz, 2 × CH_{ar}), 7.21 (2H, d, J = 8.3 Hz, 2 × CH_{ar}), 7.39−7.52 (7H, m, 7 × CH_{ar}), 7.58 (2H, d, J = 7.7 Hz, 2 × CH_{ar}), 7.71 (2H, d, J = 7.7 Hz, 2 × CH_{ar}), 7.88 (2H, d, J = 7.7 Hz, 2 × CH_{ar}), 8.06 (2H, d, J = 7.7 Hz, 2 × CH_{ar}), 11.77 [1H, s(broad), NH]; ^{19}F NMR ($CDCl_3$) δ −158.5 (1F, s, CF), −181.4 (1F, d, J = 47.4 Hz, CF), −183.4 (1F, d, J = 48.3 Hz, CF); ^{13}C NMR ($CDCl_3$) δ 12.8 (SMe), 14.3 (d, 5.8 Hz, SMe), 16.5 (d, J = 9.2 Hz, SMe), 55.3 and 55.4 (9H, s, 3 × MeO), 88.1 (d, J = 192.7 Hz, CHF), 94.6 (d, J = 192.7 Hz), 114.0 (2 × CH_{ar}), 114.2 (2 × CH_{ar}), 114.5 (2 × CH_{ar}), 120.7 (2 × CH_{ar}), 121.1 (2 × CH_{ar}), 125.8 (2 × CH_{ar}), 128.0 (2 × CH_{ar}), 128.6 (6 × CH_{ar}), 128.7 (2 × CH_{ar}), 129.1 (2 × CH_{ar}), 131.3 (CH_{ar}), 131.8 (C_{ar}), 133.7 (C_{ar}), 133.8 (CH_{ar}), 133.9 (C_{ar}), 134.1 (CH_{ar}), 137.3 (d, J = 5.8 Hz, C_{ar}), 141.6 (d, J = 5.8 Hz, C_{ar}), 142.0 [s(broad), C_{ar}], 143.3 (d, J = 199.6 Hz, CF), 152.4 (d, J = 27.7 Hz, NCS), 156.7 (OC_{ar}), 157.0 (OC_{ar}), 157.5 (OC_{ar}), 160.9 (d, J = 23.1 Hz, C═N), 162.1 (d, J = 21.9 Hz, C═N), 182.0 (d, J = 25.4 Hz, C═O), 191.3 (d, J = 21.9 Hz, C═O), 191.8 (d, J = 19.6 Hz, C═O); IR (ATR) ν 3382, 1697, 1601, 1499, 1464, 1453, 1441 cm^{-1}; MS (ES+) m/z (%) 318 ($M + H^+$, 100). Anal. Calcd for $C_{17}H_{16}FNO_2S$: C, 64.33; H, 5.08; N, 4.41. Found: C, 63.98; H, 4.89; N, 4.15.

2-Fluoro-1-(furan-2-yl)-3-(methylsulfanyl)-3-(phenylamino)-prop-2-en-1-one (enamine, 40%) and Methyl (1*Z*)-2-Fluoro-3-(furan-2-yl)-3-oxo-*N*-phenylpropanethioimidate (imines, 60%) 4c. Flash chromatography (9:1 hexane/EtOAc; R_f = 0.10) was used: 93% yield; yellow oil; ^{1}H NMR ($CDCl_3$) δ 2.27 (3H, d, J = 1.7 Hz, SMe), 2.46 [6H, s(broad), 2 × SMe], 6.01 (1H, d, J = 48.47 Hz, CHF), 6.20 (1H, d, J = 46.2 Hz, CHF), 6.56 (3H, dd, J = 3.3, 1.7 Hz, 3 × CH_{furan}), 6.78 [2H, s(broad), 2 × CH_{ar}], 6.86 [2H, s(broad), 2 × CH_{ar}], 7.09 (2H, t, J = 7.2 Hz, 2 × CH_{ar}), 7.17 (1H, t, J = 7.2 Hz, CH_{ar}), 7.25−7.38 (11H, m, 8 × CH_{ar} and 3 × CH_{furan}), 7.63 [2H, s(broad), 2 × OCH_{furan}], 7.67 (1H, s, OCH_{furan}), 11.40 [1H, s(broad), NH]; ^{19}F NMR ($CDCl_3$) δ −158.5 (1F, s, CF), −184.1 (1F, d, J = 44.7 Hz, CF), −186.4 (1F, d, J = 44.7 Hz, CF); ^{13}C NMR ($CDCl_3$) δ 12.8 (SMe), 14.1 (SMe), 16.2 (d, J = 8.1 Hz, SMe), 88.1 (d, J = 191.5 Hz, CHF), 93.1 (d, J = 197.3 Hz, CHF), 112.0 (CH), 112.1 (CH), 112.6 (CH), 118.4 (d, J = 17.3 Hz, CH), 118.9 (2 × CH), 119.7 (2 × CH), 120.5 (CH), 121.1 (CH), 123.4 (2 × CH), 124.2 (CH), 124.7 (CH), 125.1 (CH), 129.0 and 129.1 (3 × 2 × CH), 139.0 (NC_{ar}), 142.6 (d, J = 225.0 Hz, CF), 146.3 (OCH), 147.6 (OCH), 147.9 (OCH), 148.8 (2 × NC_{ar}), 149.4 and 150.0 and 150.1 (3 × C), 150.0 (d, J = 27.7 Hz, NCS), 161.6 (d, J = 21.9 Hz, 2 × C═N), 169.8 (d, J = 25.4 Hz, C═O), 179.6 and 180.2 (m, 2 × C═O); IR (ATR) ν 3135, 1697, 1590, 1567, 1541, 1484, 1459, 1414 cm^{-1}; MS (ES+) m/z (%) 278 ($M + H^+$, 100).

3-Fluoro-1,1-dimethoxy-4-(methylsulfanyl)-4-(phenylamino)-but-3-en-2-one (enamine, 32%) and Methyl 2-Fluoro-4,4-dimethoxy-3-oxo-*N*-phenylbutanethioimidate (imines, 68%) 4d. Silica gel chromatography (7:3 hexane/EtOAc; R_f = 0.32) was used: 73% yield; yellow oil; ^{1}H NMR ($CDCl_3$) δ 2.20 (3H, d, J = 2.8 Hz, SMe), 2.41−2.45 (6H, m, 2 × SMe), 3.19−3.31 (3H, m, MeO), 3.36 (6H, s, 2 × MeO), 3.42 (6H, s, 2 × MeO), 3.44 (3H, s, MeO), 4.66 (1H, s, OCHO), 4.86 (1H, s, OCHO), 5.07 (1H, d, J = 3.3 Hz, OCHO), 5.75 (1H, d, J = 47.3 Hz, CHF), 6.04 (1H, d, J = 49.0 Hz, CHF), 6.75−6.83 (4H, m, 2 × 2 × CH_{ar}), 7.02−7.10 (2H, m, 2 × CH_{ar}), 7.11−7.19 (3H, m, 3 × CH_{ar}), 7.23−7.31 (6H, m, 3 × 2 × CH_{ar}), 11.15 [1H, s(broad), NH]; ^{19}F NMR ($CDCl_3$) δ −167.3 (1F, s, CF), −187.9 (1F, d, J = 46.0 Hz, CF), −189.9 (1F, d, J = 48.7 Hz, CF); ^{13}C NMR ($CDCl_3$) δ 12.4 (SMe), 13.9 (SMe), 16.0 (d, J = 10.4 Hz, SMe), 53.5 (2 × MeO), 54.0 (2 × MeO), 54.2 (2 × MeO), 88.0 (d, J = 191.5 Hz, CHF), 91.2 (d, J = 191.5 Hz, CHF), 98.8 (OCHO), 101.9 (2 × OCHO), 118.8 (CH_{ar}), 119.0 (CH_{ar}), 119.6 (CH_{ar}), 123.4 (3 × CH_{ar}), 124.8 (CH_{ar}), 125.4 (2 × CH_{ar}), 128.7 (3 × CH_{ar}), 128.9 (3 × CH_{ar}), 138.3 (NC_{ar}), 142.1 (d, J = 221.5 Hz, CF), 148.3 (2 × NC_{ar}), 151.6 (d, J = 26.5 Hz, NCS), 162.2 (d, J = 20.8 Hz, 2 × C═N), 181.9 (d, J = 25.4 Hz, C═O), 196.7 (d, J = 17.3 Hz, 2 × C═O); IR (ATR) ν 3060, 1608, 1592, 1556, 1485 cm^{-1}; MS (ES+) m/z (%) 286 ($M + H^+$, 100).

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3-Fluoro-4-(methylsulfanyl)-4-(phenylamino)but-3-en-2-one (enamine, 40%) and Methyl 2-Fluoro-3-oxo-*N*-phenylbutanethioimidate (imines, 60%) 4g. Silica gel chromatography (9:1 hexane/EtOAc; R_f = 0.31) was used: 63% yield; yellow oil; ^{1}H NMR ($CDCl_3$) δ 2.14 (3H, d, J = 1.7 Hz, SMe), 2.17 (3H, s, CH_3CO), 2.22 (3H, d, J = 4.4 Hz, CH_3CO), 2.33 (3H, s, CH_3CO), 2.38 (6H, s, 2 × SMe), 5.41 (1H, d, J = 47.7 Hz, CHF), 5.53 (1H, d, J = 47.2 Hz, CHF), 6.82 (4H, d, J = 7.7 Hz, 2 × 2 × CH_{ar}), 7.09 (3H, t, J = 7.7 Hz, 3 × CH_{ar}), 7.18 (2H, d, J = 7.7 Hz, 2 × CH_{ar}), 7.27 (6H, t, J = 7.7 Hz, 3 × 2 × CH_{ar}), 10.65 (1H, s, NH); ^{19}F NMR ($CDCl_3$) δ −156.0 (1F, s, CF), −181.9 (1F, d, J = 47.2 Hz, CF), −182.6 (1F, d, J = 47.7 Hz, CF); ^{13}C NMR ($CDCl_3$) δ 12.3 (SMe), 13.7 (SMe), 15.6 (d, J = 8.1 Hz, SMe), 25.0 ($\underline{C}H_3CO$), 26.0 (CH_3), 90.1 (d, J = 195.0 Hz, CHF), 94.2 (d, J = 197.0 Hz, CHF), 119.6 (4 × CH_{ar}), 122.9 (2 × CH_{ar}), 124.9 (3 × CH_{ar}), 128.8 (6 × CH_{ar}), 139.2 (C_{ar}), 143.4 (d, J = 222.7 Hz, CF), 146.3 (d, J = 27.7 Hz, NCS), 148.6 (2 × C_{ar}), 161.1 (d, J = 20.8 Hz, 2 × C═N), 189.3 (d, J = 31.2 Hz, C═O), 201.4 (d, J = 26.5 Hz, 2 × C═O); IR (ATR) ν 3451, 3199, 1731, 1611, 1592, 1560, 1496, 1484 cm^{-1}; MS (ES+) m/z (%) 226 (M + H$^+$, 100).

4-Fluoro-5-phenyl-3-(phenylamino)-1*H*-pyrazole 6a. To a solution of 2-fluoro-3-(methylthio)-1-phenyl-3-(phenylamino)prop-2-en-1-one **4a** (0.70 g, 2.44 mmol) in 2-propanol (25 mL) was added 0.10 g of hydrazine (80% in water, 2.44 mmol, 1 equiv), and the mixture was heated at reflux temperature for 2 h. The solvent was evaporated in vacuo, and the obtained oil was purified by silica gel chromatography (7:3 hexane/EtOAc; R_f = 0.17) yielding 0.50 g of 4-fluoro-5-phenyl-3-phenylamino-1*H*-pyrazole **6a** (1.98 mmol, 81% yield) after recrystallization from a 1:1 hexane/Et_2O mixture: mp 181−182 °C; ^{1}H NMR (acetone-d_6) δ 6.80 (1H, t, J = 7.4 Hz, CH_{ar}), 7.22 (2H, t, J = 7.7 Hz, 2 × CH_{ar}), 7.37 (2H, d, J = 7.4 Hz, 2 × CH_{ar}), 7.38 (1H, t, J = 7.7 Hz, CH_{ar}), 7.49 (2H, t, J = 7.4 Hz, 2 × CH_{ar}), 7.53 [1H, s(broad), NH], 7.79 (2H, d, J = 7.7 Hz, 2 × CH_{ar}), 11.87 [1H, s(broad), NH]; ^{19}F NMR (acetone-d_6) δ −182.6 (1F, s, CF); ^{13}C NMR (acetone-d_6) δ 115.2 (2 × CH_{ar}), 119.1 (CH_{ar}), 125.2 and 125.3 (2 × CH_{ar}), 128.4 (CH_{ar}, C_{ar}, NC_q), 128.9 (2 × CH_{ar}), 129.1 (2 × CH_{ar}), 137.0 (d, J = 244.6 Hz, CF), 138.5 [s(broad), NC_qN], 144.1 (NC_{ar}); IR (ATR) δ 3435, 1601, 1574 cm^{-1}; MS (ES+) m/z (%) 254 (M + H$^+$, 100). Anal. Calcd for $C_{15}H_{12}FN_3$: C, 71.13; H, 4.78; N, 16.59. Found: C, 71.38; H, 4.39; N, 16.55.

4-Fluoro-3-(4-methoxyphenylamino)-5-phenyl-1*H*-pyrazole 6b. Silica gel chromatography (7:3 hexane/EtOAc; R_f = 0.20) was used: 88% yield; mp 139−140 °C (1:1 hexane/Et_2O); ^{1}H NMR (acetone-d_6) δ 3.72 (3H, s, OCH_3), 6.82 (2H, d, J = 8.5 Hz, 2 × CH_{ar}), 7.27 [1H, s(broad), NH], 7.30−7.34 (1H, m, CH_{ar}), 7.35−7.41 (2H, m, 2 × CH_{ar}), 7.49 (2H, t, J = 7.7 Hz, 2 × CH_{ar}), 7.76 (2H, d, J = 7.7 Hz, 2 × CH_{ar}), 11.60 [1H, s(broad), NH], ^{19}F NMR (acetone-d_6) δ −184.0 (1F, s, CF); ^{13}C NMR (acetone-d_6) δ 55.7 (OCH_3), 115.0 (2 × CH_{ar}), 117.6 (2 × CH_{ar}), 125.9 and 126.0 (2 × CH_{ar}), 129.1 (CH_{ar}, C_{ar}, NC_q), 129.9 (2 × CH_{ar}), 137.2 (d, J = 244.6 Hz, CF), 138.2 (NC_{ar}), 140.2 [s(broad), NC_qN], 154.2 (OC_{ar}); IR (ATR) ν 3441, 1610, 1575, 1505, 1442 cm^{-1}; MS (ES+) m/z (%) 284 (M + H$^+$, 100). Anal. Calcd for $C_{16}H_{14}FN_3O$: C, 67.83; H, 4.98; N, 14.83. Found: C, 67.60; H, 4.79; N, 14.52.

4-Fluoro-5-(furan-2-yl)-3-(phenylamino)-1*H*-pyrazole 6c. Silica gel chromatography (7:3 hexane/EtOAc; R_f = 0.17) was used: 70% yield; mp 148−149 °C (1:1 hexane/Et_2O); ^{1}H NMR (acetone-d_6) δ 6.57 (1H, dd, J = 3.5, 1.5 Hz, CH_{furan}), 6.76 (1H, d, J = 3.5 Hz, CH_{furan}), 6.81 (1H, t, J = 7.7 Hz, CH_{ar}), 7.22 (2H, t, J = 7.7 Hz, 2 × CH_{ar}), 7.35 (2H, d, J = 7.7 Hz, 2 × CH_{ar}), 7.57 [1H, s(broad), NH], 7.62 (1H, d, J = 1.5 Hz, OCH_{furan}), 11.98 [1H, s(broad), NH]; ^{19}F NMR (acetone-d_6) δ −181.7 (1F, s, CF); ^{13}C NMR (acetone-d_6) δ 107.6 (d, J = 3.5 Hz, CH_{furan}), 111.8 (CH_{furan}), 115.3 (2 × CH_{ar}), 119.4 (CH_{ar}), 121.7 [s(broad), NC_q], 129.0 (2 × CH_{ar}), 135.7 (d, J = 246.9 Hz, CF), 138.1 [s(broad), NC_qN], 142.9 (OCH_{furan}), 143.0 (OC_{furan}), 144.0 (NC_{ar}); IR (ATR) ν 3432, 1664, 1602, 1572, 1551 cm^{-1}; MS (ES+) m/z (%) 244 (M + H$^+$, 100). Anal. Calcd for $C_{13}H_{10}FN_3O$: C, 64.19; H, 4.14; N, 17.28. Found: C, 63.92; H, 3.92; N, 17.12.

5-(Dimethoxymethyl)-4-fluoro-3-(phenylamino)-1*H*-pyrazole 6d. Silica gel chromatography (7:3 hexane/EtOAc; R_f = 0.12) was used: 73% yield; mp 78−79 °C (1:1 hexane/Et_2O); white crystals; ^{1}H NMR (acetone-d_6) δ 3.35 (6H, s, 2 × OMe), 5.60 (1H, s, CH), 6.76 (1H, t, J = 7.7 Hz, CH_{ar}), 7.18 (2H, t, J = 7.7 Hz, 2 × CH_{ar}), 7.30 (2H, d, J = 7.7 Hz, 2 × CH_{ar}), 7.38 [1H, s(broad), NH], 11.36 [1H, s(broad), NH]; ^{19}F NMR (acetone-d_6) δ −183.1 (1F, s, CF); ^{13}C NMR (acetone-d_6) δ 52.5 (2 × OMe), 96.6 (d, J = 2.3 Hz, CH), 115.1 (2 × CH_{ar}), 119.2 (CH_{ar}), 126.1 (d, J = 19.6 Hz, NC_q), 128.9 (2 × CH_{ar}), 136.7 (d, J = 244.6 Hz, CF), 138.0 (d, J = 9.2 Hz, NC_qN), 144.1 (NC_{ar}); IR (ATR) ν 3401, 1597, 1569 cm^{-1}; MS (ES−) m/z (%) 250 (M − H$^+$, 100). Anal. Calcd for $C_{12}H_{14}FN_3O_2$: C, 57.36; H, 5.62; N, 16.72. Found: C, 57.52; H, 5.68; N, 16.66.

4-Fluoro-5-(4-fluorophenyl)-3-(4-methoxyphenylamino)-1*H*-pyrazole 6e. Silica gel chromatography (7:3 hexane/EtOAc; R_f = 0.10) was used: 68% yield (two steps); mp 170−171 °C (Et_2O); ^{1}H NMR (acetone-d_6) δ 3.71 (3H, s, OCH_3), 6.82 (2H, d, J = 8.8 Hz, 2 × CH_{ar}), 7.26 (2H, t, J = 8.8 Hz, 2 × CH_{ar}), 7.32 (2H, d, J = 8.8 Hz, 2 × CH_{ar}), 7.80 (2H, dd, J = 8.8, 5.5 Hz, 2 × CH_{ar}), 11.40 [1H, s(broad), NH]; ^{19}F NMR (acetone-d_6) δ −114.4 [1F, s(broad), $C_{ar}F$], −184.3 (1F, s, CF); ^{13}C NMR (acetone-d_6) δ 54.9 (OCH_3), 114.3 (2 × CH_{ar}), 115.9 (CH_{ar}), 116.2 (CH_{ar}), 116.8 (2 × CH_{ar}), 125.1 [s(broad), NC_q], 127.3 (d, J = 8.1 Hz, CH_{ar} and C_{ar}), 127.4 (d, J = 8.1 Hz, CH_{ar}), 136.3 (d, J = 243.5 Hz, CF), 137.5 (NC_{ar}), 139.0 [s(broad), NC_qN], 153.5 (OC_{ar}), 162.5 (d, J = 245.8 Hz, CF); IR (ATR) ν 3440, 1625, 1604, 1580, 1506 cm^{-1}; MS (ES+) m/z (%) 302 (M + H$^+$, 100). Anal. Calcd for $C_{16}H_{13}F_2N_3O$: C, 63.78; H, 4.35; N, 13.95. Found: C, 63.52; H, 4.17; N, 13.73.

3-(Benzylamino)-4-fluoro-5-phenyl-1*H*-pyrazole 6f. Silica gel chromatography (3:2 hexane/EtOAc; R_f = 0.27) was used: 57% yield (two steps); mp 138−139 °C (1:1 hexane/Et_2O); ^{1}H NMR (acetone-d_6) δ 4.46 (2H, s, CH_2), 5.09 [1H, s(broad), NH], 7.20 (1H, t, J = 7.5 Hz, CH_{ar}), 7.29 (2H, t, J = 7.5 Hz, 2 × CH_{ar}), 7.33 (1H, t, J = 7.5 Hz, CH_{ar}), 7.44 (2H, d, J = 7.5 Hz, 2 × CH_{ar}), 7.45 (2H, t, J = 7.5 Hz, 2 × CH_{ar}), 7.71 (2H, d, J = 7.5 Hz, 2 × CH_{ar}), 11.21 [1H, s(broad), NH], ^{19}F NMR (acetone-d_6) δ −188.2 (1F, s, CF); ^{13}C NMR (acetone-d_6) δ 47.6 (CH_2), 125.0 and 125.1 (2 × CH_{ar}), 126.7 (CH_{ar}), 127.7 (2 × CH_{ar}), 128.0 (CH_{ar} and C_{ar}), 128.2 (2 × CH_{ar}), 128.8 [s(broad), NC_q], 129.0 (2 × CH_{ar}), 135.0 (d, J = 241.4 Hz, CF), 141.0 (C_{ar}), 144.2 [s(broad), NC_qN]; IR (ATR) ν 3350, 1584 cm^{-1}; MS (ES+) m/z (%) 268 (M + H$^+$, 100). Anal. Calcd for $C_{16}H_{14}FN_3$: C, 71.89; H, 5.28; N, 15.72. Found: C, 71.51; H, 5.07; N, 15.37.

4-Fluoro-5-methyl-3-(phenylamino)-1*H*-pyrazole 6g. Silica gel chromatography (7:3 hexane/EtOAc; R_f = 0.15) was used: 82% yield; mp 132−133 °C (1:1 hexane/Et_2O); ^{1}H NMR (acetone-d_6) δ 2.21 (3H, d, J = 1.1 Hz, CH_3), 6.76 (1H, t, J = 7.7 Hz, CH_{ar}), 7.18 (2H, t, J = 7.7 Hz, 2 × CH_{ar}), 7.29 (2H, d, J = 7.7 Hz, 2 × CH_{ar}), 7.37 [1H, s(broad), NH], 11.21 [1H, s(broad), NH]; ^{19}F NMR (acetone-d_6) δ −187.9 (1F, s, CF); ^{13}C NMR (acetone-d_6) δ 7.4 (CH_3), 115.0 (2 × CH_{ar}), 118.9 (CH_{ar}), 125.0 [s(broad), NC_q], 128.9 (2 × CH_{ar}), 137.6 (d, J = 237.7 Hz, CF), 138.1 [s(broad), NC_qN], 144.4 (NC_{ar}); IR (ATR) ν 3332, 1618, 1602, 1551 cm^{-1}; MS (ES+) m/z (%) 192 (M + H$^+$, 100). Anal. Calcd for $C_{10}H_{10}FN_3$: C, 62.82; H, 5.27; N, 21.98. Found: C, 62.56; H, 5.07; N, 21.52.

3-Amino-4-fluoro-5-phenyl-1*H*-pyrazole 7. To a solution of 25 mg (0.09 mmol, 1 equiv) of 3-(benzylamino)-4-fluoro-5-phenyl-1*H*-pyrazole **6f** in 1 mL of MeOH were added 17 mg (0.28 mmol, 3 equiv) of acetic acid and 10 mg (40 wt %) of Pd-C. The mixture was stirred under a H_2 atmosphere (2.5 bar) at room temperature for 30 h. The mixture was filtered, and the solvent was evaporated to afford 16 mg of 3-aminopyrazole 7 (0.09 mmol, 94% yield): mp 96−97 °C (1:1 hexane/Et_2O); ^{1}H NMR ($CDCl_3$) δ 7.36 (1H, t, J = 7.4 Hz, CH_{ar}), 7.44 (2H, t, J = 7.4 Hz,

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2 × CH_{ar}), 7.60 (2H, d, J = 7.4 Hz, 2 × CH_{ar}); ^{19}F NMR ($CDCl_3$) δ −186.0 (1F, s, CF); ^{13}C NMR ($CDCl_3$) δ 125.2 and 125.3 (2 × CH_{ar}), 127.8 (d, J = 4.6 Hz, NC_q), 128.4 (CH_{ar}), 128.6 (C_{ar}), 129.0 (2 × CH_{ar}), 135.3 (d, J = 243.5 Hz, CF), 141.9 (d, J = 11.5 Hz, NC_qN); IR (ATR) ν 3404, 1662, 1600, 1550 cm^{-1}; MS (ES+) m/z (%) 178 ($M + H^+$, 100). Anal. Calcd for $C_9H_8FN_3$: C, 61.01; H, 4.55; N, 23.72. Found: C, 59.89; H, 4.51; N, 23.68.

4-Fluoro-5-(4-methoxyphenylamino)-1,3-diphenyl-1*H*-pyrazole 9. A solution of 5.77 g (18.20 mmol, 1 equiv) of compound **4b** and 2.16 g (20 mmol, 1.1 equiv) of phenylhydrazine in 150 mL of EtOH and AcOH (0.6 mL) was heated at reflux temperature for 24 h. The solvent was removed under reduced pressure to give the crude product that was purified by column chromatography (9:1 hexane/EtOAc; R_f = 0.17) to yield 4.97 g (13.83 mmol, 76% yield) of pyrazole **9**: ^{1}H NMR ($CDCl_3$) δ 3.76 (3H, s, OCH_3), 5.27 [1H, s(broad), NH], 6.72 (2H, d, J = 8.8 Hz, 2 × CH_{ar}), 6.82 (2H, d, J = 8.8 Hz, 2 × CH_{ar}), 7.35 (1H, t, J = 7.7 Hz, CH_{ar}), 7.42 (3H, t, J = 7.7 Hz, 3 × CH_{ar}), 7.49 (2H, t, J = 7.7 Hz, 2 × CH_{ar}), 7.63 (2H, t, J = 7.7 Hz, 2 × CH_{ar}), 8.03 (2H, d, J = 7.7 Hz, 2 × CH_{ar}); ^{19}F NMR ($CDCl_3$) δ −171.2 (1F, s, CF); ^{13}C NMR ($CDCl_3$) δ 55.5 (OCH_3), 114.8 (2 × CH_{ar}), 115.6 (2 × CH_{ar}), 123.1 (2 × CH_{ar}), 125.9 (d, J = 4.6 Hz, 2 × CH_{ar}), 127.4 (CH_{ar}), 127.7 (C_{ar}), 128.2 (CH_{ar}), 128.6 (2 × CH_{ar}), 129.1 (2 × CH_{ar}), 130.8 (d, J = 4.6 Hz, NC_q), 137.3 (NC_{ar}), 137.6 (d, J = 4.6 Hz, NC_qN), 138.6 (NC_{ar}), 141.2 (d, J = 251.5 Hz, CF), 153.8 (OC_{ar}); IR (ATR) ν 3374, 1622, 1596, 1509 cm^{-1}; MS (ES+) m/z (%) 360 ($M + H^+$, 100). Anal. Calcd for $C_{22}H_{18}FN_3O$: C, 73.52; H, 5.05; N, 11.69. Found: C, 73.72; H, 4.83; N, 12.00.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Copies of ^{1}H NMR and ^{13}C NMR spectra of all isolated new compounds (**2e**, **4a**−**d**, **4g**, **5**, **6a**−**g**, and **7**−**10**) and ^{1}H NOE NMR spectrum of **2c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308.
(2) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320.
(3) Petrov, A. V. *Fluorinated Heterocyclic Compounds: Synthesis, Chemistry, and Applications*; John Wiley & Sons: New York, 2009.
(4) Ichikawa, J.; Kobayashi, M.; Noda, Y.; Yokota, N.; Amano, K.; Minami, T. *J. Org. Chem.* **1996**, *61*, 2763.
(5) Clemens, L. *Heterocycles* **2007**, *71*, 1467.
(6) Fustero, S.; Román, R.; Sanz-Cervera, J. F.; Simón-Fuentes, A.; Cuñat, A. C.; Villanova, S.; Murguía, M. *J. Org. Chem.* **2008**, *73*, 3523 and references cited therein.
(7) Fustero, S.; Román, R.; Sanz-Cervera, J. F.; Simón-Fuentes, A.; Bueno, J.; Villanova, S. *J. Org. Chem.* **2008**, *73*, 8545.
(8) Fustero, S.; Simón-Fuentes, A.; Sanz-Cervera, J. F. *Org. Prep. Proced. Int.* **2009**, *41*, 253 and references cited therein.
(9) Pace, A.; Buscemi, S.; Vivona, N. *Org. Prep. Proced. Int.* **2007**, *39*, 1 and references cited therein.
(10) For an example, see: Skinner, P. J.; Cherrier, M. C.; Webb, P. J.; Shin, Y. J.; Gharbaoui, T.; Lindstrom, A.; Hong, V.; Tamura, S. Y.; Dang, H. T.; Pride, C. C.; Chen, R.; Richman, J. G.; Connolly, D. T.; Semple, G. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5620.
(11) Molines, H.; Wakselman, C. *J. Org. Chem.* **1989**, *54*, 5618.
(12) Sloop, J. C.; Bumgardner, C. L. *J. Fluorine Chem.* **2002**, *118*, 135.
(13) Ishihara, T.; Okada, Y.; Kuroboshi, M.; Shinozaki, T.; Ando, T. *Chem. Lett.* **1995**, 239.
(14) Zhang, Q.; Lu, L. *Tetrahedron Lett.* **2000**, *41*, 8545.
(15) Elmaati, T. M. A.; El-Taweel, F. M. *J. Heterocycl. Chem.* **2004**, *41*, 109.
(16) Anwara, H. F.; Elnagdic, M. H. *ARKIVOC* **2009**, *i*, 198.
(17) Tang, J.; Shewchuk, L. M.; Sato, H.; Hasegawa, M.; Washio, Y.; Nishigaki, N. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2985.
(18) Teng, M.; Zhu, J.; Johnson, M. D.; Chen, P.; Kornmann, J.; Chen, E.; Blasina, A.; Register, J.; Anderes, K.; Rogers, C.; Deng, Y.; Ninkovic, S.; Grant, S.; Hu, Q.; Lundgren, K.; Peng, Z.; Kania, R. S. *J. Med. Chem.* **2007**, *50*, 5253.
(19) Jagath Reddy, G.; Latha, D.; Srinivasa Rao, K. *Org. Prep. Proced. Int.* **2004**, *36*, 494.
(20) Bentley, J.; Biagetti, M.; Di Fabio, R.; Genski, T.; Guery, S.; Kopf, S. R.; Leslie, C. P.; Mazzali, A.; Melotto, S.; Pizzi, D. A.; Sabbatini, F. M.; Seri, C. PCT Int. Appl. WO 2008092888 A1 20080807, 2008.
(21) Horiuchi, Y.; Nunami, N.; Tatamidani, H.; Ohata, E. PCT Int. Appl. WO 2009020137 A1 20090212, 2009.
(22) Dressen, D.; Garofalo, A. W.; Hawkinson, J.; Hom, D.; Jagodzinski, J.; Marugg, J. L.; Neitzel, M. L.; Pleiss, M. A.; Szoke, B.; Tung, J. S.; Wone, D. W. G.; Wu, J.; Zhang, H. *J. Med. Chem.* **2007**, *50*, 5161.
(23) Large, M. S. Eur. Pat. Appl. EP 61318 A2 19820929, 1982.
(24) Ohata, S.; Kato, K.; Toriyabe, K.; Ito, Y.; Hamaguchi, R.; Nakano, Y. PCT Int. Appl. WO 2009051245 A1 20090423, 2009.
(25) Yang, C.-H. U.S. Patent Appl. US 2007054150 A1 20070308, 2007.
(26) Gorissen, J.; Viehe, H. G. *Bull. Soc. Chim. Belg.* **1978**, *87*, 391.
(27) Bogolyubskii, A. V.; Skrynnikova, A. A.; Popov, V. I.; Il'Chenko, A. Ya.; Yagupolskii, L. M. *Ukr. Khim. Zh. (Russ. Ed.)* **1989**, *55*, 420.
(28) Surmont, R.; Verniest, G.; De Kimpe, N. *Org. Lett.* **2010**, *12*, 4648.
(29) Potts, K. T.; Winslow, P. A. *Synthesis* **1987**, 839.
(30) Mahata, P. K.; Syam Kumar, U. K.; Sriram, V.; Ila, H.; Junjappa, H. *Tetrahedron* **2003**, *59*, 2631.
(31) Peruncheralathan, S.; Yadav, A. K.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2005**, *70*, 9644.
(32) Carroll, W. A.; Dart, M. J.; Kolasa, T.; Meyer, M. D.; Patel, M. V.; Wang, X. PCT Int. Appl. WO 2008063781, 2008; *Chem. Abstr.* **2008**, *149*, 9996.
(33) Ishikawa, N.; Kitazume, T. Eur. Pat. Appl. EP 154894; *Chem. Abstr.* **1986**, *104*, 148482.
(34) Yagupol'skii, L. M.; Kul'chitskii, M. M.; Il'chenko, A. Ya. *Zh. Org. Khim.* **1972**, *8*, 2182.
(35) Rudorf, W. D.; Schierhorn, A.; Augustin, M. *Tetrahedron* **1979**, *35*, 551.
(36) O'Hagan, D.; Bridge, C. F. *J. Fluorine Chem.* **1997**, *82*, 21.
(37) Kumar, A.; Aggarwal, V.; Ila, H.; Junjappa, H. *Synthesis* **1980**, 748.
(38) Sunduru, N.; Agarwal, A.; Babu Katiyar, S.; Nishi; Goyal, N.; Gupta, S.; Chauhan, P. M. S. *Bioorg. Med. Chem.* **2006**, *14*, 7706.

(39) Ohsugi, E.; Fujioka, T.; Harada, H.; Nakamura, M.; Maeda, R. *Chem. Pharm. Bull.* **1989**, *37*, 1268.
(40) Spitzner, R.; Menzel, M.; Schroth, W. *Synthesis* **1982**, 206.
(41) Singh, O. M.; Junjappa, H.; Ila, H. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3561.
(42) Choi, E. B.; Youn, I. K.; Pak, C. S. *Synthesis* **1988**, 792.
(43) Yu, H.; Dong, D.; Ouyang, Y.; Liu, Q.; Wang, Y. *Lett. Org. Chem.* **2005**, *2*, 755.
(44) Mahata, P. K.; Venkatesh, C.; Syam Kumar, U. K.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2003**, *68*, 3966.
(45) Nishio, T. *Helv. Chim. Acta* **1998**, *81*, 1207.
(46) Kohra, S.; Turuya, S.; Kimura, M.; Ogata, K.; Tominaga, Y. *Chem. Pharm. Bull.* **1993**, *41*, 1293.
(47) Verniest, G.; Van Hende, E.; Surmont, R.; De Kimpe, N. *Org. Lett.* **2006**, *8*, 4767.