

Selective, Metal-Free Approach to 3- or 5-CF₃-Pyrazoles: Solvent Switchable Reaction of CF₃-Ynones with Hydrazines

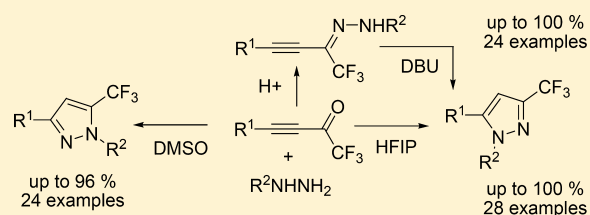
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Supporting Information

ABSTRACT: A detailed study of the reaction of trifluoroacetylated acetylenes and aryl (alkyl) hydrazines was performed, aimed to the regioselective synthesis of 3- or 5-trifluoromethylated pyrazoles. It was found that the regioselectivity of reaction depends dramatically on the solvent nature. Highly polar protic solvents (hexafluoroisopropanol) favor the formation of 3-trifluoromethylpyrazoles. In contrast, when the reaction was performed in polar aprotic solvents (DMSO), the formation of their 5-CF₃-substituted isomers was preferentially observed. Alternatively, the regioselective assembly of 3-CF₃-substituted pyrazoles can be performed via two-step one-pot procedure. The reaction of trifluoromethylated ynones with aryl (alkyl) hydrazines in the presence of acidic catalysts leads to formation of the corresponding hydrazones. The latter can be smoothly transformed into 3-CF₃-pyrazoles by treatment with a base. This solvent-switchable procedure was used for the preparation of such important drugs as Celebrex and SC-560 as well as their isomers in gram scale. The possible reaction mechanism is discussed.



INTRODUCTION

Over the recent decade the chemistry of fluorinated heterocycles has enjoyed a lot of attention due to the wide application of these derivatives as pharmaceuticals, agrochemicals and high utility for further design of biologically active compounds.¹ The pyrazole core is a privileged structural unit of modern drugs and agrochemicals.² A very important task in this field is to incorporate selectively the fluorine-containing groups into proper place of this heterocyclic ring to discover new biologically active candidates for drug design.³ Thus, a lot of fluorinated pyrazoles exhibited the various types of biological activity and found the applications as medicines and agrochemicals (Figure 1). Nevertheless, there is a significant demand for the searching of new methods for the selective preparation of CF₃-substituted pyrazoles.⁴

In the recent years many approaches toward trifluoromethylated pyrazoles were developed. The modern methodologies for the synthesis of pyrazoles bearing fluorine or fluorine-containing functional group at various positions of this heterocyclic molecule were analyzed very recently.^{4d} Generally, CF₃-substituted pyrazoles are obtained by a traditional method based on condensation of 1,3-diketones with hydrazines.¹ However, despite the high yields of the target heterocycles this method suffers from a very important drawback: when asymmetrical ketones were treated with monosubstituted hydrazines, a mixture of hardly separable regioisomers was formed as a rule.⁵ In spite of significant progress in this field, the use of acetylenic or β -functionally substituted unsaturated fluorine-containing ketones (as synthetic equivalents of 1,3-diketones) is more efficient approach affording the target

heterocycles in good yield. Thus, a series of 3- and 5-polyfluoroalkylpyrazoles were synthesized from β -functionally substituted enones and hydrazines.⁶ The synthesis of N-unsubstituted CF₃-pyrazoles based on trifluoromethylated ynones and hydrazine hydrate was also reported.⁷ The reaction with monosubstituted hydrazines a priori can give a mixture of isomeric pyrazoles to be dependent on the reaction conditions and the structure of starting compounds. A search for efficient methods for the selective formation of CF₃-pyrazoles is still a significant challenge of modern organic synthesis. Very recently, the preferential formation of either 3- or 5-CF₃-pyrazoles from ynones and aryl hydrazines was reported under the catalytic or catalyst-free conditions.⁸ Herein, we report the general and highly efficient method for the selective preparation of 3- and 5-trifluoromethylpyrazoles based on the solvent-switchable reaction of CF₃-ynones and alkyl and aryl hydrazines and the study of the reaction mechanism.

RESULTS AND DISCUSSION

To start our study, a model reaction of ynone **1a** with phenylhydrazine **2a** was investigated in various solvents at room temperature (Scheme 1). Trifluoroacetylated acetylene **1a** has highly polarized triple bond activated for nucleophilic addition and highly electrophilic carbonyl group. Therefore, both 1,2- and 1,4-addition of hydrazine can be expected to result in different regiochemistry of formed pyrazoles. The reaction progress was monitored by ¹⁹F NMR. It was found

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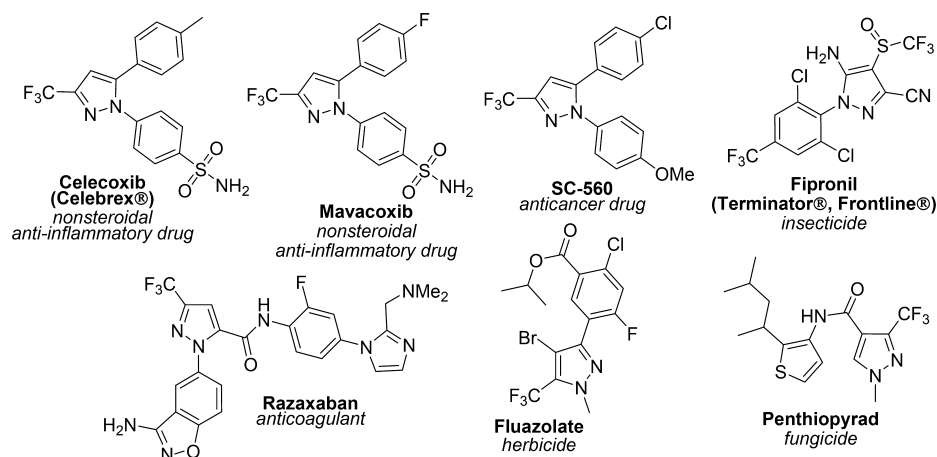
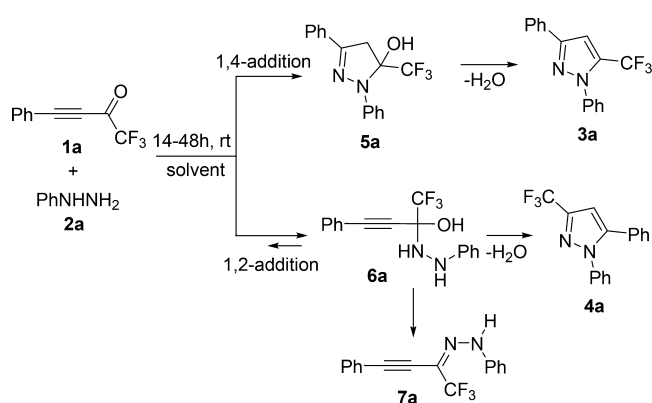


Figure 1. Some examples of bioactive CF_3 -pyrazoles.

Scheme 1. Reaction of Ynone 1a with Phenylhydrazine 2a in Different Solvents



that reaction is extremely sensitive to the solvent nature and led almost in all cases to a mixture of five principal products in

varying ratios: the target 5- and 3-trifluoromethylpyrazoles **3a** and **4a**, pyrazoline **5a**, hemiaminal **6a**, and hydrazone **7a** (Table 1). Structures of all these compounds were determined unambiguously by ^1H , ^{13}C , and ^{19}F NMR data (see SI). Moreover, NMR data of **3a**, **4a**, **5a** are in agreement with literature data.^{3,8}

These preliminary results revealed the complicated nature of the reaction. However, the intermediates **5a**, **6a**, and **7a** can be regarded as precursors of pyrazoles **3a** and **4a**. Therefore, to achieve a full conversion we used heating of the reaction mixture with *p*-TSA (Table 1). After this treatment a much simpler picture of the products ratio was observed: the reaction mixture contained **3a** and **4a** only.

It was found that the solvent nature influenced very significantly the products ratio and the reaction selectivity. Thus, the reaction under solvent-free conditions as well as in polar aprotic solvents (DMSO, DMF, HMPA, THF, MeCN) led mostly to pyrazoline **5a**, which can be further converted into 5- CF_3 -pyrazole **3a** by heating at 80 °C in the presence of

Table 1. Composition of the Reaction Mixture by ^{19}F NMR Data

entry	solvent	compound (^{19}F NMR chemical shift, ppm)				
		3a (−58.5)	4a (−63.2)	5a (−80.5)	6a (−82.5)	7a (−67.1)
1	DMSO	0(97) ^a	3(3)	84/97 ^b (0)	13/0 (0)	0(0)
2	DMF	2(97)	3(3)	95(0)	0(0)	0(0)
3	HMPA	1(24)	11	77/88(68)	11/0(0)	0(0)
4	THF	0/8(87)	8(8)	57/79(0)	30/0(0)	5(5)
5	MeCN	1(76)	24(24)	74(0)	2/0(0)	0(0)
6	neat	28(70)	27(27)	42(0)	0(0)	3(3)
7	Et_3N	0	8/30	8/66	84/4	0
8	$\text{Me}_2\text{N}(\text{CH}_2)_2\text{OH}$	1	11	88	0	0
9	CHCl_3	28	66	0	2/0	4
10	PhMe	11(36)	62(62)	25(0)	4/0(0)	2(2)
11	Hexane	2(26)	73(73)	24(0)	2/0(0)	1(1)
12	NH_2CHO	1(32)	68(68)	31(0)	0(0)	0(0)
13	<i>t</i> -BuOH	19	67	12	0	2
14	$\text{HO}(\text{CH}_2)_2\text{OH}$	0(13)	87(87)	13(13)	0(0)	0(0)
15	MeOH	0(20)	80(80)	20(0)	0(0)	0(0)
16	EtOH	12	88	0	0	0
17	HFIP	2	98	0	0	0
18	AcOH	3	30	0	0	67
19	$\text{THF}+\text{BF}_3\cdot\text{Et}_2\text{O}$	0	3	0	0	97

^aYields obtained after heating of the reaction mixture with *p*-TSA are given in parentheses. ^bComposition of the reaction mixture after 14 h/48 h.

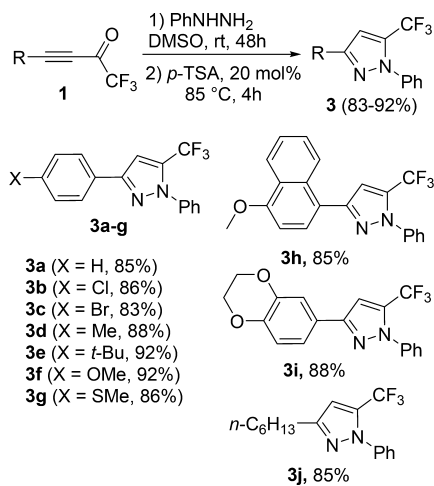
the catalytic amounts of *p*-TSA. The highest selectivity was observed for the reaction in DMSO and DMF which afforded (97:3) a mixture of isomers **3a** and **4a** (Table 1, entry 1). We have chosen DMSO as a nontoxic solvent for further research due to its simpler work up procedures and NMR reaction control. More basic solvents such as Et₃N and Me₂N-(CH₂)₂OH afforded preferentially **5a**. In contrast, the reaction in nonpolar medium (hexane, toluene, CHCl₃) and polar protic solvents (fluorinated and nonfluorinated alcohols) resulted in 3-CF₃-isomer **4a** preferentially. The best regioselectivity was observed when hexafluoroisopropanol (HFIP) was used as the reaction media (Table 1, entry 17). However, the corresponding hydrazone **7a** was obtained mostly (AcOH) or exclusively (BF₃·Et₂O in THF) when the reaction was catalyzed by Lewis or Brønsted acids. It is important to note that the formed hydrazone **7a** is stable under these conditions: heating of the obtained reaction mixture at 80 °C during 5–7 h did not lead to the cyclization of hydrazone **7a** into pyrazole **4a**. It is also very interesting to point out that hemiaminal **6a** (initially formed in polar aprotic solvents) was transformed into pyrazole **4a** and pyrazoline **5a** instead of hydrazone **7a** after standing of the reaction mixture at room temperature for 48 h. That means that there is equilibrium between starting ketone **1a** and hemiaminal **6a**.

According to these preliminary data, DMSO provided highly controlled formation of 5-CF₃-pyrazole **3a**, whereas 3-CF₃-pyrazole can be prepared selectively using HFIP as the reaction media. Thus, at the first stage of the study, the possibility to control the regioselectivity of the reaction (formation of either 3-CF₃-pyrazoles or 5-CF₃-pyrazoles) by a proper choice of the solvent was demonstrated.

Having in hand the optimal reaction conditions for the selective formation of each isomer, the synthetic scope of the reaction was studied. A number of ynones bearing both aryl and alkyl substituents at the triple bond was treated with phenylhydrazine in DMSO for 2 days at room temperature followed by heating at 85 °C with *p*-TSA for 4 h. As a result, a number of 5-CF₃ pyrazoles **3a–j** was prepared in high isolated yields (Scheme 2).

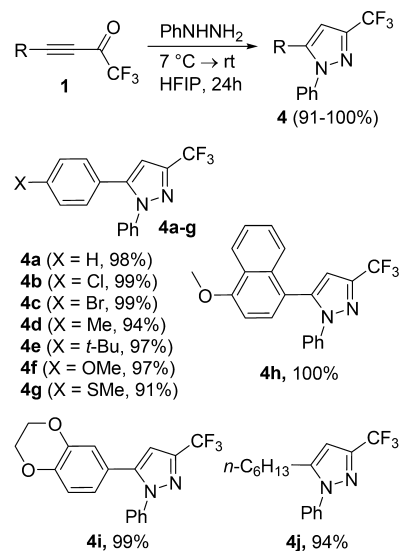
The reaction of ketones **1a–j** with phenylhydrazine in HFIP showed even better results to give isomeric 3-CF₃-pyrazoles **4a–j** in excellent yield and regioselectivity. It should be noted

Scheme 2. Scope of the Reaction of Ynones 1 with Phenylhydrazine To Form 5-CF₃-Pyrazoles 3



that the reaction in HFIP was found to be highly sensitive to the temperature of the reagents mixing due to significant exothermicity of the reaction. When the starting materials were mixed at room temperature, admixture of minor isomer **3** was formed in 5–9% yield. However, simple precooling down to 7 °C of the initial ketone solution minimized the share of the minor isomer to ~2% in all cases. Moreover, minor isomers are easily separable by column chromatography or recrystallization (Scheme 3).

Scheme 3. Scope of the Reaction of Ynones 1 with Phenylhydrazine To Form 3-CF₃-Pyrazoles 4



The configuration of isomeric pyrazoles **3j** and **4j** with aliphatic substituent was determined on the basis of the concerted application of ¹H–¹H 2D homonuclear experiment NOESY and ¹H–¹³C 2D heteronuclear experiment HMBC (Figure 2). Thus, intensive cross peaks between the resonance

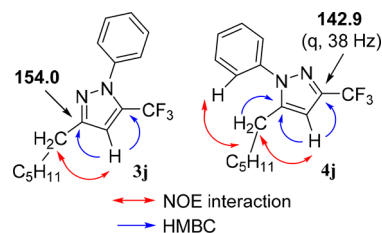


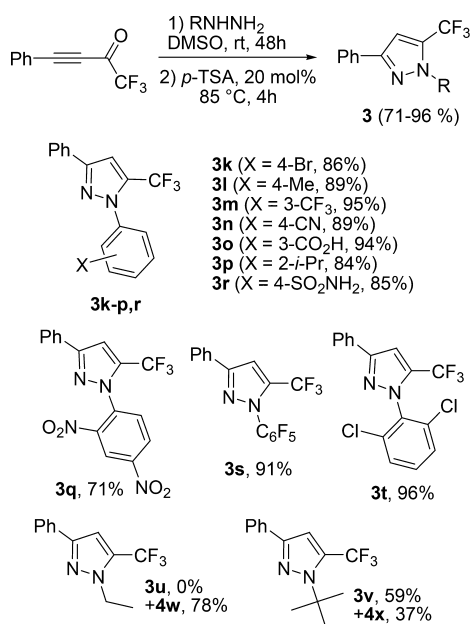
Figure 2. Main NOESY and HMBC correlations for pyrazoles **3j and **4j**.**

signals of the C⁵CH₂ group and both *ortho* protons of the benzene ring and olefinic proton were observed in the spectrum of isomer **4j**. In contrast, the presence of intensive NOE peak between olefinic and methylene protons along with the absence of any NOE between protons of the aromatic and alkyl groups was revealed in minor isomer **3j**. Moreover, the structure of two isomeric trifluoromethylated pyrazoles was additionally confirmed by ¹⁹F NMR spectra.^{5,6f}

Next, the influence of hydrazine component on the reaction scope was examined. Aryl hydrazines bearing both electron-donating and electron-withdrawing substituents in the aromatic ring were evaluated in the reaction with ynone **1a**. Similarly to phenylhydrazine **2a**, hydrazines **2b–j** reacted with ynone **1a** in

DMSO to afford 5-trifluoromethylpyrazoles **3k–t** in high yields and selectivity (Scheme 4). The reaction tolerates a wide

Scheme 4. Scope of the Reaction of 1a with Various Hydrazines 2 To Form 5-CF₃-Pyrazoles

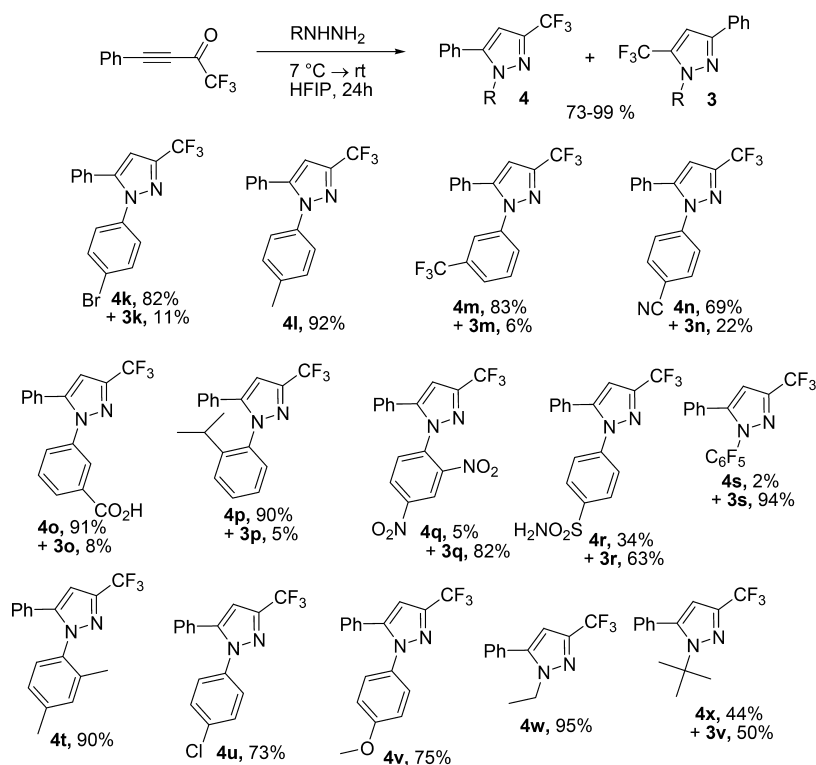


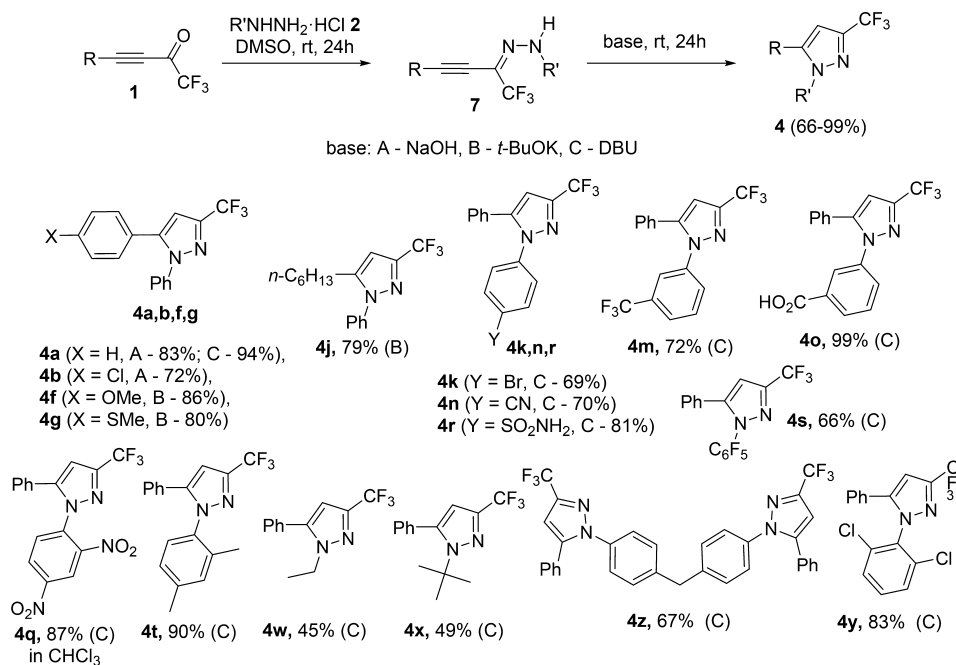
variety of substituents (*ortho*-isopropyl, 2,6-dichloro, pentafluoro) and functional groups (CO₂H, SO₂NH₂, CN) in the aryl moiety of hydrazine. 5-Trifluoromethylated pyrazole **3s** was formed exclusively in the case of the reaction with pentafluorophenylhydrazine **2e**. As a rule, in all cases the corresponding 3-substituted isomer **4** was formed as a minor

admixture (in amounts less than 1–2%). It should be noted, that the reaction with most electron-poor 2,4-dinitrophenylhydrazine **2j** under the same conditions afforded a mixture of pyrazole **3q** (71%), the corresponding hydrazone **7b** (7%) and pyrazole **4q** (7%) (Scheme 4). However, single recrystallization permits to obtain pure product **3q** very easily. Surprisingly, the reaction with *tert*-butylhydrazine led to a mixture of pyrazoles **3v** and **4x** in 3:2 ratio and the reaction with ethylhydrazine did not give 5-CF₃-pyrazole **3u** at all to form only 3-CF₃-pyrazole **4w** in 78% yield. Such reversed selectivity can be explained by a higher nucleophilicity of nitrogen attached to the alkyl substituent in contrast to the aryl hydrazines.

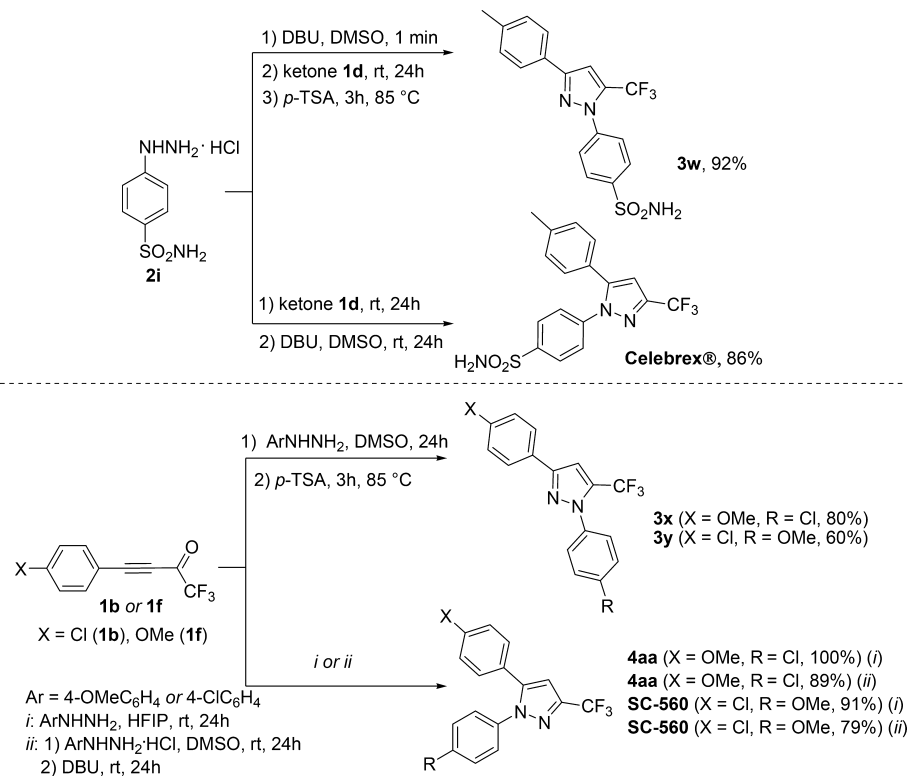
It was found that the reaction in HFIP was much more sensitive to the hydrazine structure. Thus, the reaction of the aryl hydrazines bearing electron donating substituents in the phenyl ring led to 3-CF₃-pyrazoles **4** highly regioselectively (Scheme 5). To our delight, the reaction with highly nucleophilic ethylhydrazine afforded regioselectively 3-CF₃-pyrazole **4w** in spite of the fact that both nitrogens in starting hydrazine have similar nucleophilicity. At the same time the reaction with more bulky *tert*-butylhydrazine led to a mixture of regioisomeric pyrazoles **3v** and **4x** in nearly 1:1 ratio. Increase of electron withdrawing properties of the substituents in the aryl group of hydrazine resulted in raise of 5-CF₃-pyrazole **3** fraction in the mixture of CF₃-pyrazole products. Moreover, in the case of highly electron-poor 2,4-dinitrophenyl-, 4-aminosulfonylphenyl-, and polyfluorophenylhydrazine the corresponding 5-CF₃-isomers **3q,r,s** became the major reaction products (isolated yields 82, 63, and 94% correspondingly). The reaction with pentafluorophenyl- and 2,4-dinitrophenylhydrazines afforded also the corresponding hydrazones (9% and 12%) and only 4% and 2% of pyrazoles **4q,s** (Scheme 5). Therefore, this approach was found to be most applicable for the selective preparation of 3-CF₃-pyrazoles **4** with the highly nucleophilic

Scheme 5. Scope of the Reaction of 1a with Various Hydrazines To Form 3-CF₃-Pyrazoles 4



Scheme 6. Synthesis of 3-CF₃-Pyrazoles **4** via Intermediate Formation of Hydrazones

Scheme 7. Synthesis of Celebrex, SC-560, and Their Regioisomers



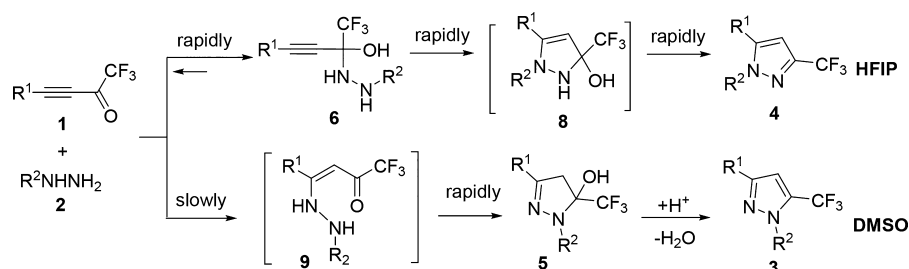
aryl and alkyl hydrazines. The reaction has the significant restrictions in terms of regioselectivity for less nucleophilic hydrazines bearing EWGs.

Since hydrazines bearing strongly electron-withdrawing groups have shown poor selectivity in the reactions with ynones **1**, we decided to find an alternative possibility for the selective assembly of the target CF₃-pyrazoles having more electron-deficient aryl ring at the nitrogen. This is an especially important problem due to a number of current drugs and drug

candidates (Celebrex and its analogues) having such substituents at the position 1 of the pyrazole core.⁹

We found that the problem can be solved very efficiently by the use of the acidic catalysts in the reaction of ynones **1** with hydrazines **2**. The selective formation of the corresponding hydrazones **7** was observed under these particular conditions (Table 1, entries 18–19). It has been reported that acetylenic hydrazones can be transformed into pyrazoles by the treatment with a base^{4c,10} or by the transition metals¹¹ catalysis. Taking

Scheme 8. Possible Mechanism of the Reaction



into account these data, we assumed that the similar cyclization can be used for the transformation of hydrazones 7 into the target CF_3 -pyrazoles.

Hydrazones 7 were easily prepared in situ by the reaction of ketones 1 with aryl hydrazine hydrochlorides $2 \times \text{HCl}$ in DMSO at room temperature; their formation was confirmed by ^{19}F NMR spectroscopy. Next, different reaction conditions were examined for the cyclization of intermediate hydrazones. It was found that this reaction proceeds efficiently in the presence of the strong inorganic (NaOH) or organic ($t\text{-BuOK}$, DBU) bases to give the target pyrazoles 4 in high yield and excellent selectivity. Both the electron-rich and electron-poor hydrazones were successfully involved in the reaction (Scheme 6). It was found that the scope of such approach was wide enough to be applicable for the bulky substituents as well as the various functional groups in the structure of both starting hydrazine and ynone. Alkyl hydrazines were also successfully involved into the transformation to form only 3- CF_3 -pyrazoles 4w (ethyl) and 4x (*tert*-butyl) in good yields. The attempt to carry out the reaction with the most electron-poor 2,4-dinitrophenylhydrazine resulted in severe tarring in DMSO. However, the treatment of hydrazone 7b with DBU in CHCl_3 led to pyrazole 4q in 87% yield. Hydrazone 7b was easily prepared by the reflux of ynone 1a with 2,4-dinitrophenylhydrazine in 5 M solution of HCl in MeOH .

As a result, the additional solvent-switchable procedure for the assembly of CF_3 -pyrazoles was elaborated. Using this approach Celebex and SC-560 as well as the corresponding regioisomers can be prepared very efficiently (Scheme 7). The principle advantage of this approach is its flexibility and simplicity. Very efficient switching of the reaction direction with total regiocontrol was provided by the sequence of the same reagents added in a one-pot (ynone 1d, hydrazine 2i, DMSO, DBU) procedure. For example, when DBU was first added to the solution of hydrochloride of 4-aminosulfonylphenylhydrazine 2i in DMSO followed by the addition of ketone 1d, the 5-trifluoromethylated pyrazole 3w was formed selectively. Alternatively, Celebex can be synthesized by the reaction of hydrazine 2i as hydrochloride with ynone 1d to form intermediate hydrazone. The subsequent addition of DBU resulted in cyclization into the target drug molecule. We demonstrated that all these syntheses can be performed in gram scale without any restrictions.

We even were able to find two types of conditions for the selective synthesis of SC-560 and its isomer 4aa. Since the electron rich 4-methoxy- and 4-chlorophenylhydrazines were used in this case, the reaction can be performed either directly in HFIP or in DMSO via intermediate hydrazone formation. Both methods provided very high yields of the target compounds. It is important to note that the preparation of regioisomeric pyrazoles 3x and 3y is also possible. In this case, a

one-pot reaction in DMSO followed by heating with *p*-TSA resulted in 5-trifluoromethylated products 3x and 3y in 80% and 60% yields correspondingly. It should be noted, that there is confusion with the structure of SC-560 in the literature. In some recent articles^{4a,c,12} isomer 4aa (chlorine in the aryl adjacent to N(1) atom, methoxy group in the aryl adjacent to C(5) atom) is named as SC-560, which is not correct. The correct structure vice versa has chlorine in aryl adjacent to C(5) atom and methoxy group in the aryl moiety adjacent to N(1)^{8,13} (Scheme 7, Figure 1).

A possible pathway for the selective formation of either pyrazoles 3 or 4 is shown in Scheme 8. ^{19}F NMR monitoring of the reaction of phenylhydrazine 2a with ketone 1a in HFIP revealed the fast consumption of the starting substrate (80% after 2 min and full consumption after 30 min) accompanied by a parallel formation of pyrazole 3a and minor amounts of isomeric pyrazole 4a (Figure 3). No intermediates were observed in the course of the reaction: all these transformations proceeded very quickly.

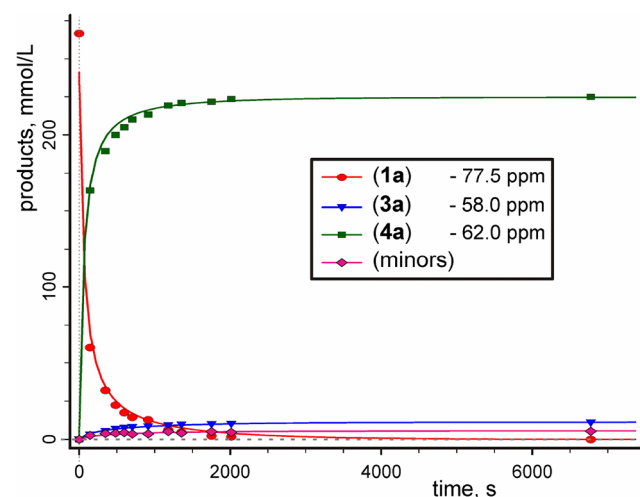


Figure 3. Monitoring of the reaction of ynone 1a with phenylhydrazine in HFIP.

To get a clue about the reaction mechanistic scheme, we studied a slower reacting system such as ynone 1e with phenylhydrazine 2a in CDCl_3 . It was found that the first step of the transformation is a nucleophilic addition of phenylhydrazine 2a to the carbonyl group of ynone 1, which led to the formation of hemiaminal intermediate 6b (Figure 4). This step of the reaction sequence proceeded rapidly to give a 1:3 mixture (^{19}F NMR) of the starting ketone 1e with adduct 6b in 1 min at rt. The structure of 6b was elucidated by analysis of both NMR and IR spectra. Only two singlets of *tert*-butyl group

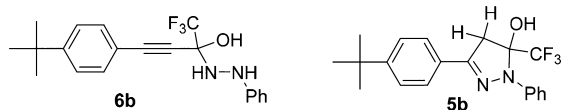


Figure 4. Structures of intermediates **5b** and **6b**.

(the initial ynone **1** and new compound in the ratio 1:3) were presented in the ^1H NMR spectrum of the reaction mixture, while no signals of olefinic protons were observed. At the same time, in ^{13}C NMR spectrum two new singlets of C_{sp} atoms (82.2 and 87.8 ppm) as well as new quartet of quaternary carbon center (82.6 ppm, $J = 32$ Hz) were detected. The appearance of a new peak in the ^{19}F NMR spectrum at -82.5 ppm is also in agreement with the proposed structure. Finally, the IR spectrum of this mixture shows two strong bands in the $\text{C}\equiv\text{C}$ stretching region: at 2201 cm^{-1} for ketone **1e** and 2240 cm^{-1} as well as a band of the OH group at 3589 cm^{-1} for intermediate **6b**. As the reaction proceeded, the intensity of the signal at -82.5 ppm decreased while the intensity of two new signals of pyrazole **4e** (-62.4 ppm) and pyrazoline **5b** (-78.4 ppm) increased.

The structure of **5b** was assigned by the comparison of its ^{19}F and ^1H NMR spectra with those of pyrazoline **5a**. The most characteristic signals in ^1H NMR spectra are doublets of the AB system of the methylene protons at 3.59 and 3.73 ppm ($J = 17.8$ Hz). Disappearance of these signals accompanied by the growing of the minor pyrazole **3e** signal value in ^{19}F NMR spectrum (-57.9 ppm) also proved its structure as well as the last step of cascade transformation leading to isomer **3e**. Additionally, the structures of two principle intermediates **5b** and **6b** (Figure 4) were confirmed by 2D NMR experiments ($^1\text{H}-^{13}\text{C}$ HMBC and $^1\text{H}-^{15}\text{N}$ HMBC). Thus, for structure **6b** correlations in 2D $^1\text{H}-^{15}\text{N}$ HMBC spectra allowed to assign the signals of H_α aromatic protons of PhNH group (7.03 ppm) by the cross-peak with the signal of nitrogen atom (PhNH) resonating at -291.7 ppm. The narrow singlet in ^1H NMR spectra (4.52 ppm) belongs to the second NH proton and has the coupling constant $^1J(\text{H},\text{N}) = 80$ Hz with signal at -289.5 ppm and cross-peak with signal resonating at -291.7 ppm. Moreover, correlations of NH proton singlet with carbon signals at 82.6 and 87.8 ppm in 2D spectra $^1\text{H}-^{13}\text{C}$ HMBC, which allow the assigning signals in ^{13}C NMR spectra. The chemical shifts of nitrogen atoms in ^{15}N NMR of structure **5b** were assigned by the correlations with CH_2 protons: -47.4 ppm ($\text{C}=\text{N}$), -222.9 ppm (NPh). At the end of the monitoring only the signals of pyrazoles **3e** (-57.9 ppm) and **4e** (-62.4 ppm) were observed in the ^{19}F NMR.

The reaction of ynone **1a** with phenylhydrazine in $\text{DMSO}-d_6$ was also very fast. We observed no signals of the starting ketone **1a** even after 1–2 min from the beginning of the NMR monitoring (Figure 5). Surprisingly, only hemiaminal **6a** (-80.5 ppm) and pyrazolinol **5a** (-78.8 ppm) were found in the reaction mixture. Moreover, conversion of **6a** into **5a** was observed in the course of monitoring to give pyrazoline **5a** as the only product in about 10 h. The structure of hemiaminal **6a** was confirmed by the formation of hydrazone **7a** after addition of MeSO_3H and heating up to 80°C for 2 h of the reaction mixture, which was obtained by the standing of **1a** and phenylhydrazine for 10 min at rt. These manipulations led to a mixture of pyrazole **3a** and hydrazone **7a** in the ratio equal to that of pyrazoline **5a** and hemiaminal **6a** (26:74).

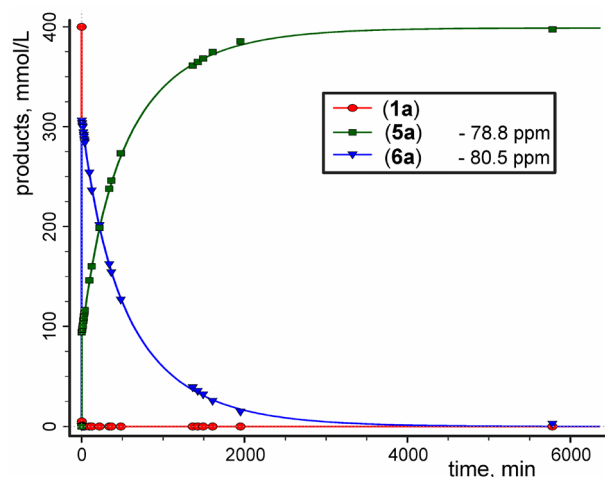
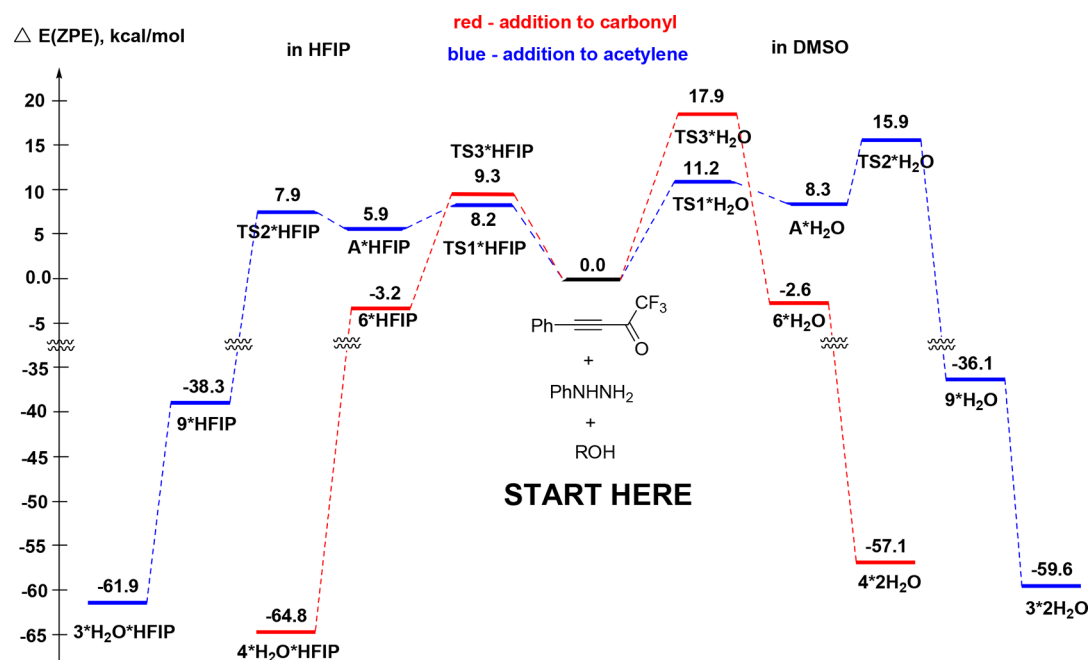
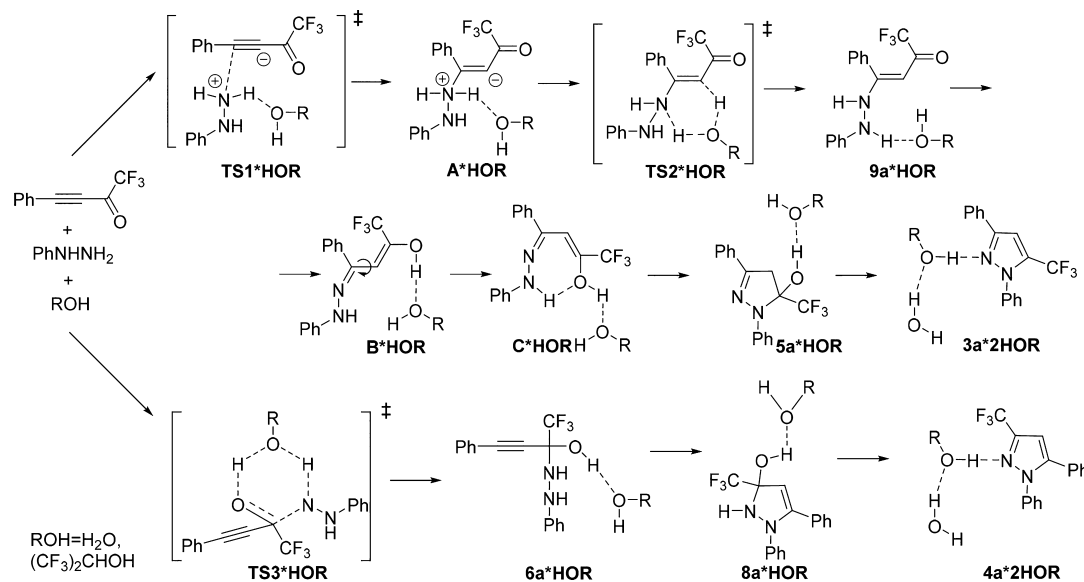


Figure 5. Monitoring of the reaction of **1a** with phenylhydrazine in $\text{DMSO}-d_6$.

The following scheme of the reaction can be proposed on the basis of NMR monitoring data obtained (Scheme 8). The hydrazine addition to the carbonyl group leads rapidly to hemiaminal **6** both in DMSO and HFIP. Next, the fast intramolecular cyclization of **6** takes place in HFIP to form pyrazole **4** probably through the intermediate formation of pyrazoline **8**. In contrast, in DMSO hemiaminal **6** dissociates back to ketone **1** and hydrazine **2**, and their slow recombination gives enone **9**, which then rapidly undergoes the intramolecular cyclization to pyrazoline **5**. These conclusions are also in good agreement with nature of the used solvents. Most probably, highly acidic HFIP activates carbonyl group of ketone by protonation of oxygen (see, for example,¹⁴ and references therein). On the contrary, the aprotic and highly polar DMSO is coordinated at highly polar carbonyl group to enhance its efficient steric bulkiness and to direct nucleophile (aryl hydrazine) to the triple bond of ynone. On the other hand the proton source is necessary for heterocyclization of **6** into pyrazole **4**. In the absence of proton in DMSO the reverse reaction of hemiaminal **6** takes place.

To rationalize the reasons of the observed regioselectivity of the reaction by the nature of the solvent, the quantum chemical modeling of the reaction of ketone **1a** with phenylhydrazine **2a** in HFIP and DMSO was performed. The calculations were carried out using Gaussian 09 software by DFT B3LYP with 6-311+G** basis.¹⁵ The solvent effect was investigated by the polarized continuum model (PCM model), a specific solvation was accounted by including of HFIP molecule (in case of HFIP) and molecule of H_2O (in case of DMSO originated from dehydration step). As a reasonable preposition, we postulated that the initial attack of hydrazine on the carbonyl group triggers the reaction sequence leading to the 3- CF_3 -pyrazole **4a**. In contrast, Michael addition of hydrazine to the triple bond of ynone initiates the process to give 5- CF_3 -pyrazole **3a** (Schemes 8, 9).

Diagrams of the energy changes for the most important steps of the reaction are presented on Figure 6. In the case of the reaction in DMSO, the calculations showed that the addition energy to the triple bond ($\text{TS1}^*\text{H}_2\text{O}$) is 6.7 kcal/mol lower than the addition energy to the carbonyl group ($\text{TS3}^*\text{H}_2\text{O}$), which makes the addition to the triple bond more preferential. As a result, the reaction in DMSO should lead to 5- CF_3 -pyrazole **3a**. The similar calculation for HFIP revealed no

Scheme 9. Probable Reaction Pathways in DMSO (ROH = H₂O) and HFIP (ROH = HFIP)Figure 6. $\Delta E(\text{ZPE})$ (kcal/mol) by B3LYP/6-311+G(d,p) for the reaction in HFIP and DMSO.

significant difference of the corresponding transition states for the competitive processes ($\text{TS1}^*\text{HFIP}$) and ($\text{TS3}^*\text{HFIP}$), allowing the addition to carbonyl to take place. Probably, using more accurate models for accounting of the solvent effect, better accordance of the calculated and experimental data can be achieved. We made some additional calculations with participation of one molecule DMSO for proton transfer instead of water. In this case the barrier of TS1 dropped from 11.2 to 8.3 kcal/mol. Also energies of adducts **A** and **9a** were found to be ~ 3 kcal/mol lower. The obtained results show that in HFIP the formation of pyrazole **4a** is more favorable by 2.9 kcal/mol compared to formation of **3a**. The opposite situation is observed in DMSO where pyrazole **3a** is more stable by 2.5 kcal/mol.

CONCLUSIONS

It was found that the reaction of trifluoromethylated ynone with aryl (alkyl) hydrazines can be directed selectively either to 3- CF_3 -pyrazoles or 5- CF_3 -pyrazoles. The reaction route can be totally controlled by the solvent nature. The activation of the carbonyl group by very polar protic solvents such as fluorinated alcohols leads to formation of 3- CF_3 -substituted pyrazoles. In contrast, polar aprotic solvents (DMSO, DMF) coordinate with the carbonyl group to enhance its efficient steric bulkiness and to direct nucleophile to the triple bond of ynone. The acidic catalysis favors the formation of hydrazones, transformed easily into 3- CF_3 -substituted pyrazoles by the treatment with a base. As a result, this study provided an efficient tool for the selective preparation of trifluoromethylated pyrazoles. The utility of the elaborated methods was confirmed by the gram scale synthesis

of known pyrazole drugs Celebex and SC-560 as well as the corresponding regioisomeric molecules.

EXPERIMENTAL SECTION

NMR spectra were recorded at 600.2 and 400.1 (^1H), 150.9 and 100.6 (^{13}C), 40.6 (^{15}N), 564.7, 376.3, and 282.4 (^{19}F) MHz respectively from solutions in CDCl_3 and $\text{DMSO}-d_6$. Chemical shifts (δ) in ppm are reported with the use of the residual chloroform (7.25 for ^1H and 77.0 for ^{13}C), dimethyl sulfoxide (2.49 for ^1H and 39.5 for ^{13}C) as internal references. The coupling constants (J) are given in Hertz (Hz). The ^{15}N and ^{19}F chemical shifts were referenced to CH_3NO_2 and CFCl_3 , respectively. The IR spectra were recorded with a Bruker Vertex 70 FT-IR spectrometer and with a portable Varian 3100 diamond ATR/FT-IR spectrometer. The films of solid products for IR spectra are prepared by vaporization of corresponding solutions. The GC-MS analyses were performed with a Shimadzu GCMS-QP5050A instrument (EI, 70 eV). The silica gel used for flash chromatography was 230–400 mesh. HRMS spectra were measured at MicroTof Bruker Daltonics and Orbitrap Elite instrument. All reagents were of reagent grade and were either used as such or distilled prior to use. All solvents were dried by standard procedures and freshly distilled prior to use.

Synthesis of CF_3 -ynones 1 (General Procedure). Preheated 500 mL three-necked round-bottom flask equipped with thermometer, dropping funnel (with rubber septum) and argon inlet was purged with argon and then charged with 200 mL of dry THF and 0.1 mol of corresponding terminal acetylene. Thus, obtained solution was cooled to -60°C and 0.11 mol of *n*-BuLi (44 mL, 2.5 M solution in hexane) was added dropwise. The reaction mixture was allowed to warm up to -20°C and then was cooled to -60°C . Next, $\text{CF}_3\text{CO}_2\text{Et}$ was added slowly at temperature lower than -50°C . The reaction mixture was allowed to warm up to room temperature (15 – 20°C) and then quenched with ~ 100 mL of 2 M HCl at 0 – 20°C . Organic layer was separated and water phase was extracted with CH_2Cl_2 (3×30 mL). Combined extracts were washed with water (50 mL), dried over Na_2SO_4 and volatiles were evaporated in vacuo. The residue was purified by vacuum distillation, recrystallization or by passing through short silica gel pad using appropriate hexane– CH_2Cl_2 mixtures as an eluent.

1,1,1-Trifluoro-4-phenylbut-3-yn-2-one (1a). Purified by vacuum distillation (bp = 76 – $79^\circ\text{C}/10$ Torr). Colorless oil (17.42 g, 88% yield). ^1H NMR (400.1 MHz, CDCl_3) δ 7.43–7.47 (m, 2H, Ph), 7.54–7.59 (m, 1H, Ph), 7.66–7.69 (m, 2H, Ph). The NMR data are in agreement with previously reported.¹⁶

4-(4-Chlorophenyl)-1,1,1-trifluorobut-3-yn-2-one (1b). Purified by passing through short silica gel pad (hexane– CH_2Cl_2 3:1). Pale yellow crystals, mp 40 – 42°C (14.61 g, 62% yield). ^1H NMR (400.0 MHz, CDCl_3) δ 7.43 (d, $J_{\text{HH}} = 8.5$ Hz, 2H), 7.61 (d, $J_{\text{HH}} = 8.5$ Hz, 2H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 84.0, 98.9, 114.8 (q, $J_{\text{CF}} = 288.2$ Hz, CF_3), 116.5, 129.5, 135.1, 139.3, 167.0 (q, $J_{\text{CF}} = 42.4$ Hz, $\text{C}=\text{O}$). The NMR data are in agreement with previously reported.¹⁷

4-(4-Bromophenyl)-1,1,1-trifluorobut-3-yn-2-one (1c). Purified by vacuum distillation (bp = 113 – $116^\circ\text{C}/10$ Torr). Colorless crystals, mp 44 – 46°C (15.43 g, 56% yield). ^1H NMR (400.1 MHz, CDCl_3) δ 7.53 (d, $J_{\text{HH}} = 8.4$ Hz, 2H, Ar), 7.60 (d, $J_{\text{HH}} = 8.4$ Hz, 2H, Ar). ^{13}C NMR (100.6 MHz, CDCl_3) δ 84.0, 98.9, 114.8 (q, $J_{\text{CF}} = 288.6$ Hz, CF_3), 116.9, 127.8, 132.4, 135.1, 167.1 (q, $J_{\text{CF}} = 42.4$ Hz, $\text{C}=\text{O}$). ^{19}F NMR (376.3 MHz, CDCl_3) δ -77.8 . IR (ν , cm^{-1}) 1699 ($\text{C}=\text{O}$), 2197 ($\text{C}\equiv\text{C}$). HRMS (ESI-TOF) m/z [$\text{M} + \text{OH}$] $^-$ Calcd for $\text{C}_{10}\text{H}_5\text{BrF}_3\text{O}_2^-$: 292.9431, found 292.9432.

1,1,1-Trifluoro-4-*p*-tolylbut-3-yn-2-one (1d). Purified by passing through short silica gel pad (hexane– CH_2Cl_2 3:1). Yellow oil (15.96 g, 75% yield). ^1H NMR (400.1 MHz, CDCl_3) δ 2.43 (s, 3H, CH_3), 7.26 (d, $J_{\text{HH}} = 8.4$ Hz, 2H, Ar), 7.57 (d, $J_{\text{HH}} = 8.4$ Hz, 2H, Ar). ^{13}C NMR (100.6 MHz, CDCl_3) δ 21.8, 83.5, 101.5, 114.9 (q, $J_{\text{CF}} = 288.6$ Hz, CF_3), 115.0, 129.7, 134.0, 143.8, 167.1 (q, $J_{\text{CF}} = 42.0$ Hz, $\text{C}=\text{O}$). ^{19}F NMR (376.3 MHz, CDCl_3) δ -78.7 . IR (ν , cm^{-1}) 1698 ($\text{C}=\text{O}$), 2195 ($\text{C}\equiv\text{C}$). The NMR data are in agreement with previously reported.⁸

4-(4-*tert*-Butylphenyl)-1,1,1-trifluorobut-3-yn-2-one (1e). Purified by passing through short silica gel pad (hexane– CH_2Cl_2 3:1). Pale yellow crystals, mp 48 – 50°C (15.20 g, 60% yield). ^1H NMR (400.1 MHz, CDCl_3) δ 1.33 (s, 9H, *t*-Bu), 7.46 (d, $J_{\text{HH}} = 8.3$ Hz, 2H, Ar), 7.61 (d, $J_{\text{HH}} = 8.3$ Hz, 2H, Ar). ^{13}C NMR (100.6 MHz, CDCl_3) δ 30.9, 35.3, 83.5, 101.5, 114.9 (q, $J_{\text{CF}} = 288.0$ Hz, CF_3), 115.0, 126.1, 134.0, 156.7, 167.2 (q, $J_{\text{CF}} = 41.0$ Hz, $\text{C}=\text{O}$). The NMR data are in agreement with previously reported.¹⁶

1,1,1-Trifluoro-4-(4-methoxyphenyl)but-3-yn-2-one (1f). Purified by passing through short silica gel pad (hexane– CH_2Cl_2 3:1). Yellow oil (15.78 g, 69% yield). ^1H NMR (400.1 MHz, CDCl_3) δ 3.86 (s, 3H, OCH_3), 6.93 (d, $J_{\text{HH}} = 8.9$ Hz, 2H, Ar), 7.62 (d, $J_{\text{HH}} = 8.9$ Hz, 2H, Ar). ^{13}C NMR (100.6 MHz, CDCl_3) δ 55.5, 84.1, 102.5, 109.6, 114.8, 115.0 (q, $J_{\text{CF}} = 288.2$ Hz, CF_3), 136.3, 163.2, 167.0 (q, $J_{\text{CF}} = 41.7$ Hz, $\text{C}=\text{O}$). The NMR data are in agreement with previously reported.¹⁶

1,1,1-Trifluoro-4-(4-methylthio)phenyl)but-3-yn-2-one (1g). Purified by passing through short silica gel pad (hexane– CH_2Cl_2 3:1). Brown-yellow crystals, mp 31 – 33°C (9.81 g, 40% yield). ^1H NMR (400.1 MHz, CDCl_3) δ 2.52 (s, 3H, SCH_3), 7.24 (d, $J_{\text{HH}} = 8.4$ Hz, 2H, Ar), 7.56 (d, $J_{\text{HH}} = 8.4$ Hz, 2H, Ar). ^{13}C NMR (100.6 MHz, CDCl_3) δ 14.3, 84.2, 101.4, 113.2, 114.8 (q, $J_{\text{CF}} = 288.6$ Hz, CF_3), 125.1, 134.0, 146.4, 166.8 (q, $J_{\text{CF}} = 42.0$ Hz, $\text{C}=\text{O}$). ^{19}F NMR (376.3 MHz, CDCl_3) δ -78.6 . IR (ν , cm^{-1}) 1689 ($\text{C}=\text{O}$), 2180 ($\text{C}\equiv\text{C}$). HRMS (ESI-TOF) m/z [$\text{M} + \text{OH}$] $^-$ Calcd for $\text{C}_{11}\text{H}_8\text{F}_3\text{O}_2\text{S}^-$: 261.0203, found 261.0203.

1,1,1-Trifluoro-4-(1-methoxynaphthalen-4-yl)but-3-yn-2-one (1h). Purified by recrystallization from hexane. Yellow crystals, mp 73 – 75°C (18.57 g, 67% yield). ^1H NMR (400.1 MHz, CDCl_3) δ 4.00 (s, 3H, OCH_3), 6.69 (d, $^3J_{\text{HH}} = 8.2$ Hz, 1H, Ar), 7.51 (dt, $^3J_{\text{HH}} = 8.0$ Hz, $^4J_{\text{HH}} = 0.8$ Hz, 1H, Ar), 7.61 (dt, $^3J_{\text{HH}} = 8.0$ Hz, $^4J_{\text{HH}} = 0.8$ Hz, 1H, Ar), 7.78 (d, $^3J_{\text{HH}} = 8.2$ Hz, 1H, Ar), 8.11 (d, $^3J_{\text{HH}} = 8.0$ Hz, 1H, Ar), 8.24 (d, $^3J_{\text{HH}} = 8.0$ Hz, 1H, Ar). ^{13}C NMR (100.6 MHz, CDCl_3) δ 55.8, 88.9, 101.9, 103.9, 107.0, 115.2 (q, $J_{\text{CF}} = 289.0$ Hz, CF_3), 122.8, 124.8, 125.1, 126.4, 128.8, 134.8, 137.3, 160.0, 166.7 (q, $J_{\text{CF}} = 41.6$ Hz, $\text{C}=\text{O}$). ^{19}F NMR (376.3 MHz, CDCl_3) δ -78.0 . IR (ν , cm^{-1}) 1678 ($\text{C}=\text{O}$), 2175 ($\text{C}\equiv\text{C}$). HRMS (ESI-TOF) m/z [$\text{M} + \text{H}$] $^+$ Calcd for $\text{C}_{15}\text{H}_{10}\text{F}_3\text{O}_2^+$: 279.0627, found 279.0624.

1,1,1-Trifluoro-4-(2,3-dihydrobenzo[*b*][1,4]dioxin-7-yl)but-3-yn-2-one (1i). Purified by recrystallization from hexane. Pale yellow crystals, mp 83 – 85°C (15.38 g, 60% yield). ^1H NMR (400.1 MHz, CDCl_3) δ 4.24–4.31 (m, 4H, $\text{OCH}_2\text{CH}_2\text{O}$), 6.87 (d, $J_{\text{HH}} = 8.9$ Hz, 1H, Ar), 7.13–7.18 (m, 2H, Ar). ^{13}C NMR (100.6 MHz, CDCl_3) δ 64.0, 64.7, 83.4, 102.0, 110.2, 114.9 (q, $J_{\text{CF}} = 288.6$ Hz, CF_3), 118.2, 123.0, 128.4, 143.7, 148.2, 166.9 (q, $J_{\text{CF}} = 41.6$ Hz, $\text{C}=\text{O}$). ^{19}F NMR (376.3 MHz, CDCl_3) δ -78.7 . IR (ν , cm^{-1}) 1687 ($\text{C}=\text{O}$), 2186 ($\text{C}\equiv\text{C}$). HRMS (ESI-TOF) m/z [$\text{M} + \text{Na}$] $^+$ Calcd for $\text{C}_{12}\text{H}_7\text{F}_3\text{O}_3\text{Na}^+$: 279.0239, found 279.0235.

1,1,1-Trifluorodec-3-yn-2-one (1j). Purified by vacuum distillation (bp = 71 – $73^\circ\text{C}/12$ Torr). Colorless oil (16.29 g, 79% yield). ^1H NMR (400.1 MHz, CDCl_3) δ 0.89 (t, $J_{\text{HH}} = 6.7$ Hz, 3H), 1.25–1.34 (m, 4H), 1.42 (pent, $J_{\text{HH}} = 7.3$ Hz, 2H), 1.63 (pent, $J_{\text{HH}} = 7.3$ Hz, 2H), 2.49 (t, $J_{\text{HH}} = 7.1$ Hz, 2H). The NMR data are in agreement with previously reported.¹⁸

Reaction of Ketone 1a with Phenylhydrazine 2a in Various Solvents (General Procedure). A 3 mL screw neck vial was charged with corresponding solvent (1 mL), ketone 1a (99 mg, 0.5 mmol) and phenylhydrazine 2a (56 mg, 0.53 mmol), and maintained for appropriate time (see main text). Next, *p*-TSA (17 mg, 0.1 mmol) was added and reaction mixture was heated at 80°C for 4 h. Reaction progress was monitored by ^{19}F NMR. Probes for ^{19}F NMR were prepared by diluting aliquote with CDCl_3 . The yields and ratio of products were determined by ^{19}F NMR as well (with the use of C_6F_6 or 4-chlorobenzotrifluoride as internal standard) (see Table 1).

5-(Trifluoromethyl)-1,3-diphenyl-1H-pyrazole (3a). Pale brown powder, mp 55 – 57°C (Lit. data¹⁹ 53 – 54°C). ^1H NMR (400.1 MHz, CDCl_3) δ 7.14 (s, 1H, CH_{pyr}), 7.37–7.42 (m, 1H), 7.44–7.55 (m, 5H), 7.57–7.61 (m, 2H), 7.89–7.92 (m, 2H). ^{19}F NMR (376.3 MHz, CDCl_3) δ -58.7 . The NMR data are in agreement with previously reported.¹⁹

3-(Trifluoromethyl)-1,5-diphenyl-1H-pyrazole (4a). Light yellow powder, mp 85–87 °C (Lit. data²⁰ 86–88 °C). ¹H NMR (400 MHz, CDCl₃) δ 6.75 (s, 1H, C⁴H); 7.15–7.40 (m, 10H, Ph). ¹³C NMR (100.6 MHz, CDCl₃) δ 105.7 (q, J = 2 Hz, C⁴), 121.5 (q, J = 269 Hz, CF₃), 125.7, 128.6, 128.8, 129.0, 129.1, 129.3, 129.4, 139.4 (2 Ph), 143.4 (q, J = 38 Hz, C³), 144.9 (C⁵). ¹⁹F NMR (376.5 MHz, CDCl₃) δ –62.5. IR (KBr, cm⁻¹) ν 1154, 1165 (C–F), 1557, 1596, 1645 (C=C, C=N, Ph). The NMR data are in agreement with previously reported.^{4c}

5-(Trifluoromethyl)-4,5-dihydro-1,3-diphenyl-1H-pyrazol-5-ol (5a). This compound was not isolated and NMR data were obtained from reaction mixture in DMSO. ¹H NMR (400.1 MHz, DMSO-*d*₆) δ 3.57 (d, J_{HH} = 18.9 Hz, 1H), 3.87 (d, J_{HH} = 18.9 Hz, 1H), 7.00 (td, J_{HH} = 7.2 Hz, J_{HH} = 1.1 Hz, 1H), 7.29 (td, J_{HH} = 7.4 Hz, J_{HH} = 1.6 Hz, 2H), 7.38–7.50 (m, 5H), 7.75 (dd, J_{HH} = 8.1 Hz, J_{HH} = 1.5 Hz, 2H), 8.22 (br s, 1H, OH). ¹³C NMR (100.6 MHz, DMSO-*d*₆) δ 44.0, 93.1 (q, J_{CF} = 31.7 Hz, C–CF₃), 118.8, 121.1 (q, J_{CF} = 290.8 Hz, CF₃), 122.0, 125.6, 128.3, 128.7, 129.1, 131.4, 142.5, 146.7. ¹⁹F NMR (376.3 MHz, DMSO-*d*₆) δ –78.8. The NMR data are in agreement with previously reported.³

1,1,1-Trifluoro-4-phenyl-2-(2-phenylhydrazino)but-3-yn-2-ol (6a). This compound was not isolated and NMR data were obtained from reaction mixture in Et₃N. ¹H NMR (400.1 MHz, CDCl₃) δ 4.02 (s, 1H), 5.34 (s, 1H), 6.22–6.27 (m, 2H), 6.47–6.51 (m, 4H), 6.62–6.69 (m, 4H), 6.71–6.76 (m, 1H). ¹³C NMR (100.6 MHz, CDCl₃) δ 81.0 (q, J_{CF} = 31.3 Hz, C–CF₃), 82.7, 85.1, 112.2, 117.7, 120.4, 121.8 (q, J_{CF} = 287.5 Hz, CF₃), 127.1, 127.7, 127.8, 130.6, 149.0. ¹⁹F NMR (376.3 MHz, CDCl₃) δ –82.6.

(E)-2-(1,1,1-Trifluoro-4-phenylbut-3-yn-2-ylidene)-1-phenylhydrazine (7a). Pale yellow-green needles, mp 99–101 °C (Lit. data¹⁹ 97–99 °C). ¹H NMR (400.1 MHz, DMSO-*d*₆) δ 7.01 (td, J_{HH} = 6.6 Hz, J_{HH} = 2.0 Hz, 1H), 7.30–7.38 (m, 4H), 7.47–7.54 (m, 3H), 7.70–7.74 (m, 2H), 10.86 (br s, 1H, NH). ¹³C NMR (100.6 MHz, DMSO-*d*₆) δ 75.6, 104.2, 112.1 (q, J_{CF} = 38.0 Hz, C–CF₃), 114.6, 120.5, 121.1 (q, J_{CF} = 270.9 Hz, CF₃), 122.5, 128.8, 129.2, 130.2, 132.0, 142.8. ¹⁹F NMR (376.3 MHz, DMSO-*d*₆) δ –64.9. HRMS (ESI-TOF) *m/z* [M + H]⁺ Calcd for C₁₆H₁₂F₃N₂⁺: 289.0947, found 289.0948.

Synthesis of Pyrazoles 3 by the Reaction of Ketones 1 with Hydrazines 2 in DMSO (General Procedure). A 3 mL screw neck vial was charged with DMSO (2 mL), aryl hydrazine 2* (1.05 mmol), corresponding ketone 1 (198 mg, 1 mmol), and maintained for 2 days at room temperature. Next, *p*-TSA (34 mg, 0.2 mmol) was added and reaction mixture was heated at 80–85 °C for 4 h. After that reaction mixture was poured into ~0.1 M solution of HCl (50 mL), extracted with CH₂Cl₂ (3 × 20 mL). The combined organic phase was washed with water (50 mL), dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography on silica gel using appropriate mixtures of hexane and CH₂Cl₂ (2:1–1:1, 3a–3m, 3p, 3s, 3t, 3v, 3x, 3y), CH₂Cl₂ (3n, 3q), or mixture of CH₂Cl₂ and MeOH (30:1, 3o, 3r, 3w). Aryl hydrazine was generated in situ by mixing of equivalent amounts of aryl hydrazine hydrochloride and DBU.

5-(Trifluoromethyl)-1,3-diphenyl-1H-pyrazole (3a). Pale brown powder (244 mg, 85% yield). The characterization data (mp and NMR) are given in previous section.

3-(4-Chlorophenyl)-5-(trifluoromethyl)-1-phenyl-1H-pyrazole (3b). Pale yellow crystals, mp 62–64 °C (278 mg, 86% yield). ¹H NMR (600.2 MHz, CDCl₃) δ 7.10 (s, 1H, CH_{pyr}), 7.44 (d, J_{HH} = 8.4 Hz, 2H, 4-ClC₆H₄), 7.51–7.55 (m, 3H, Ph), 7.61 (d, J_{HH} = 6.6 Hz, 2H, Ph), 7.84 (d, J_{HH} = 8.4 Hz, 2H, 4-ClC₆H₄). ¹³C NMR (150.9 MHz, CDCl₃) δ 105.9 (q, J_{CF} = 2.2 Hz, CH_{pyr}), 119.6 (q, J_{CF} = 268.5 Hz, CF₃), 125.5, 127.0, 128.9, 129.0, 129.3, 130.2, 133.9 (q, J_{CF} = 39.6 Hz, C–CF₃), 134.4, 139.0, 150.4. ¹⁹F NMR (564.7 MHz, CDCl₃) δ –58.7. The NMR data are in agreement with previously reported.³

3-(4-Bromophenyl)-5-(trifluoromethyl)-1-phenyl-1H-pyrazole (3c). Light yellow needles, mp 62–64 °C (305 mg, 83% yield). ¹H NMR (400.1 MHz, CDCl₃) δ 7.08 (s, 1H, CH_{pyr}), 7.48–7.52 (m, 3H), 7.54–7.58 (m, 4H), 7.74 (d, J_{HH} = 8.6 Hz, 2H). ¹³C NMR (100.6 MHz, CDCl₃) δ 105.9 (q, J_{CF} = 2.2 Hz, CH_{pyr}), 119.6 (q, J_{CF} = 269.1 Hz, CF₃), 122.7, 125.6, 127.3, 129.1, 129.3, 130.7, 131.9, 133.0 (q, J_{CF}

= 39.4 Hz, C–CF₃), 139.0, 150.5. ¹⁹F NMR (282.4 MHz, CDCl₃) δ –58.8. HRMS (ESI-TOF) *m/z* [M + H]⁺ Calcd for C₁₆H₁₁BrF₃N₂⁺: 367.0052, found 367.0059.

5-(Trifluoromethyl)-1-phenyl-3-*p*-tolyl-1H-pyrazole (3d). Pale yellow crystals, mp 61–64 °C (266 mg, 88% yield). ¹H NMR (400.1 MHz, CDCl₃) δ 2.43 (s, 3H, Me), 7.13 (s, 1H, CH_{pyr}), 7.29 (d, J_{HH} = 8.0 Hz, 2H, 4-MeC₆H₄), 7.48–7.55 (m, 3H, Ph), 7.60–7.64 (m, 2H, Ph), 7.83 (d, J_{HH} = 8.0 Hz, 2H, 4-MeC₆H₄). ¹³C NMR (100.6 MHz, CDCl₃) δ 21.1, 105.8 (q, J_{CF} = 1.8 Hz, CH_{pyr}), 119.8 (q, J_{CF} = 269.4 Hz, CF₃), 125.6, 125.7, 128.9, 129.0, 129.1, 129.4, 133.7, (q, J_{CF} = 39.1 Hz, C–CF₃), 138.5, 139.2, 151.7. ¹⁹F NMR (282.4 MHz, CDCl₃) δ –58.5. The NMR data are in agreement with previously reported.¹⁹

3-(4-tert-Butylphenyl)-5-(trifluoromethyl)-1-phenyl-1H-pyrazole (3e). Pale yellow oil (317 mg, 92% yield). ¹H NMR (600.2 MHz, CDCl₃) δ 1.45 (s, 9H, *t*-Bu), 7.18 (s, 1H, CH_{pyr}), 7.49–7.55 (m, 3H, Ph), 7.56 (d, J_{HH} = 8.4 Hz, 2H, 4-*t*-BuC₆H₄), 7.65 (d, J_{HH} = 7.3 Hz, 2H, Ph), 7.91 (d, J_{HH} = 8.4 Hz, 2H, 4-*t*-BuC₆H₄). ¹³C NMR (150.9 MHz, CDCl₃) δ 31.2, 34.6, 105.9 (q, J_{CF} = 2.2 Hz, CH_{pyr}), 119.8 (q, J_{CF} = 268.5 Hz, CF₃), 125.5, 125.6, 125.7, 128.9, 129.0, 129.1, 133.6 (q, J_{CF} = 38.5 Hz, C–CF₃), 139.2, 151.6, 151.7. ¹⁹F NMR (564.7 MHz, CDCl₃) δ –58.5. ¹⁵N NMR (40.6 MHz, CDCl₃) δ –169.5, –68.6. HRMS (ESI-TOF) *m/z* [M + H]⁺ Calcd for C₂₀H₂₀F₃N₂⁺: 345.1573, found 345.1573.

5-(Trifluoromethyl)-3-(4-methoxyphenyl)-1-phenyl-1H-pyrazole (3f). Pale brown crystals, mp 76–78 °C (Lit. data¹⁹ mp 77–78 °C) (293 mg, 92% yield). ¹H NMR (600.2 MHz, CDCl₃) δ 3.86 (s, 3H, MeO), 7.03 (d, J_{HH} = 8.8 Hz, 2H, 4-MeOC₆H₄), 7.10 (s, 1H, CH_{pyr}), 7.50–7.55 (m, 3H, Ph), 7.64 (d, J_{HH} = 7.3 Hz, 2H, Ph), 7.88 (d, J_{HH} = 8.8 Hz, 2H, 4-MeOC₆H₄). ¹³C NMR (150.9 MHz, CDCl₃) δ 55.0, 105.5 (q, J_{CF} = 2.2 Hz, CH_{pyr}), 114.1, 119.7 (q, J_{CF} = 268.5 Hz, CF₃), 124.4, 125.6, 127.0, 129.0, 129.1, 133.6 (q, J_{CF} = 38.5 Hz, C–CF₃), 139.2, 151.4, 160.0. ¹⁹F NMR (564.7 MHz, CDCl₃) δ –58.5. The NMR data are in agreement with previously reported.¹⁹

5-(Trifluoromethyl)-3-(4-(methylthio)phenyl)-1-phenyl-1H-pyrazole (3g). Pale brown crystals, mp 83–84 °C (287 mg, 86% yield). ¹H NMR (600.2 MHz, CDCl₃) δ 2.50 (s, 3H, MeS), 7.10 (s, 1H, CH_{pyr}), 7.33 (d, J_{HH} = 8.4 Hz, 2H, 4-MeSC₆H₄), 7.48–7.52 (m, 3H, Ph), 7.59 (d, J_{HH} = 7.3 Hz, 2H, Ph), 7.82 (d, J_{HH} = 8.4 Hz, 2H, 4-MeSC₆H₄). ¹³C NMR (150.9 MHz, CDCl₃) δ 15.3, 105.7 (q, J_{CF} = 2.2 Hz, CH_{pyr}), 119.6 (q, J_{CF} = 269.6 Hz, CF₃), 125.5, 126.0, 126.3, 128.3, 128.9, 129.1, 133.6 (q, J_{CF} = 39.6 Hz, C–CF₃), 139.1, 139.2, 151.0. ¹⁹F NMR (564.7 MHz, CDCl₃) δ –58.6. HRMS (ESI-TOF) *m/z* [M + H]⁺ Calcd for C₁₇H₁₃F₃N₂S⁺: 335.0824, found 335.0825.

5-(Trifluoromethyl)-3-(1-methoxynaphthalen-4-yl)-1-phenyl-1H-pyrazole (3h). Pale yellow oil (313 mg, 85% yield). ¹H NMR (600.2 MHz, CDCl₃) δ 4.03 (s, 3H, MeO), 6.90 (d, J_{HH} = 8.1 Hz, 1H), 7.19 (s, 1H, CH_{pyr}), 7.50–7.53 (m, 1H), 7.55–7.58 (m, 2H), 7.59–7.61 (m, 1H), 7.64–7.66 (m, 1H), 7.73–7.75 (m, 3H), 8.48 (d, J_{HH} = 8.1 Hz, 1H), 8.66 (d, J_{HH} = 8.4 Hz, 1H). ¹³C NMR (150.9 MHz, CDCl₃) δ 55.3, 103.3, 109.5 (q, J_{CF} = 2.2 Hz, CH_{pyr}), 119.9 (q, J_{CF} = 268.5 Hz, CF₃), 121.9, 122.2, 125.2, 125.3, 125.6, 125.7, 127.1, 127.8, 129.0, 129.1, 131.9, 132.9 (q, J_{CF} = 38.5 Hz, C–CF₃), 139.2, 151.7, 156.0. ¹⁹F NMR (564.7 MHz, CDCl₃) δ –58.2. HRMS (ESI-TOF) *m/z* [M + H]⁺ Calcd for C₂₁H₁₅F₃N₂O⁺: 369.1209, found 369.1209.

5-(Trifluoromethyl)-3-(2,3-dihydrobenzo[*b*][1,4]dioxin-7-yl)-1-phenyl-1H-pyrazole (3i). Pale yellow oil (305 mg, 88% yield). ¹H NMR (600.2 MHz, CDCl₃) δ 4.25 (s, 4H, –OCH₂CH₂O–), 6.94 (d, J_{HH} = 8.2 Hz, 1H), 7.03 (s, 1H, CH_{pyr}), 7.37 (dd, J_{HH} = 8.2 Hz, J_{HH} = 2.0 Hz, 1H), 7.43 (d, J_{HH} = 2.0 Hz, 1H), 7.45–7.51 (m, 3H, Ph), 7.57 (d, J_{HH} = 7.7 Hz, 2H, Ph). ¹³C NMR (150.9 MHz, CDCl₃) δ 64.2, 64.3, 105.7 (q, J_{CF} = 2.2 Hz, CH_{pyr}), 114.7, 117.5, 119.0, 119.7 (q, J_{CF} = 269.6 Hz, CF₃), 125.2, 125.5, 129.0, 129.1, 133.6 (q, J_{CF} = 38.5 Hz, C–CF₃), 139.1, 143.7, 144.1, 151.2. ¹⁹F NMR (564.7 MHz, CDCl₃) δ –58.6; HRMS (ESI-TOF) *m/z* [M + H]⁺ Calcd for C₁₈H₁₃F₃N₂O₂⁺: 347.1002, found 347.0996.

5-(Trifluoromethyl)-3-hexyl-1-phenyl-1H-pyrazole (3j). Pale yellow oil (252 mg, 85% yield). ¹H NMR (600.2 MHz, CDCl₃) δ 0.89 (t, J_{HH} = 7.0 Hz, 3H), 1.30–1.35 (m, 4H), 1.38–1.43 (m, 2H), 1.71 (pent, J_{HH} = 7.8 Hz, 2H), 2.70 (t, J_{HH} = 7.8 Hz, 2H), 6.61 (s, 1H, CH_{pyr}), 7.41 (pent, J_{HH} = 7.2 Hz, 1H), 7.43 (t, J_{HH} = 7.2 Hz, 2H), 7.48

(d, $J_{HH} = 7.2$ Hz, 2H). ^{13}C NMR (150.9 MHz, CDCl_3) δ 13.9, 22.5, 27.9, 28.9, 29.3, 31.5, 107.6 (q, $J_{CF} = 2.2$ Hz, CH_{pyr}), 119.9 (q, $J_{CF} = 268.5$ Hz, CF_3), 125.5, 128.8, 128.9, 132.8 (q, $J_{CF} = 39.6$ Hz, C- CF_3), 139.2, 153.7. ^{19}F NMR (564.7 MHz, CDCl_3) δ -58.5. HRMS (ESI-TOF) m/z $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{16}\text{H}_{19}\text{F}_3\text{N}_2^+$: 297.1573, found 297.1574. The NMR data are in agreement with previously reported.²¹

1-(4-Bromophenyl)-5-(trifluoromethyl)-3-phenyl-1H-pyrazole (3k). Pale yellow needles, mp 62–64 °C (316 mg, 86% yield). ^1H NMR (600.2 MHz, CDCl_3) δ 7.13 (s, 1H, CH_{pyr}), 7.38–7.42 (m, 1H, Ph), 7.43–7.48 (m, 4H, Ph), 7.64 (d, $J_{HH} = 8.6$ Hz, 2H, 4- BrC_6H_4), 7.89 (d, $J_{HH} = 8.6$ Hz, 2H, 4- BrC_6H_4). ^{13}C NMR (150.9 MHz, CDCl_3) δ 106.4 (q, $J_{CF} = 2.2$ Hz, CH_{pyr}), 119.6 (q, $J_{CF} = 269.4$ Hz, CF_3), 123.1, 125.7, 127.0, 128.7, 128.8, 131.4, 132.2, 133.6 (q, $J_{CF} = 39.4$ Hz, C- CF_3), 138.1, 151.8. ^{19}F NMR (564.7 MHz, CDCl_3) δ -58.6. HRMS (ESI-TOF) m/z $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{16}\text{H}_{10}\text{BrF}_3\text{N}_2^+$: 367.0052, found 367.0050.

5-(Trifluoromethyl)-3-phenyl-1-p-tolyl-1H-pyrazole (3l). Pale yellow crystals, mp 64–66 °C (269 mg, 89% yield). ^1H NMR (600.2 MHz, CDCl_3) δ 2.47 (s, 3H, Me), 7.16 (s, 1H, CH_{pyr}), 7.34 (d, $J_{HH} = 8.1$ Hz, 2H, 4- MeC_6H_4), 7.40–7.44 (m, 1H, Ph), 7.46–7.53 (m, 4H, Ph), 7.94 (d, $J_{HH} = 8.1$ Hz, 2H, 4- MeC_6H_4). ^{13}C NMR (150.9 MHz, CDCl_3) δ 21.0, 105.8 (q, $J_{CF} = 1.8$ Hz, CH_{pyr}), 119.8 (q, $J_{CF} = 269.1$ Hz, CF_3), 125.5, 125.7, 128.5, 128.7, 129.6, 131.8, 133.7 (q, $J_{CF} = 39.1$ Hz, C- CF_3), 136.7, 139.4, 151.4. ^{19}F NMR (564.7 MHz, CDCl_3) δ -58.7. HRMS (ESI-TOF) m/z $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{17}\text{H}_{13}\text{F}_3\text{N}_2^+$: 303.1104, found 303.1108.

5-(Trifluoromethyl)-1-(3-(trifluoromethyl)phenyl)-3-phenyl-1H-pyrazole (3m). Pale yellow oil (338 mg, 95% yield). ^1H NMR (400.1 MHz, CDCl_3) δ 7.17 (s, 1H, CH_{pyr}), 7.39–7.43 (m, 1H), 7.47 (t, $J_{HH} = 7.5$ Hz, 2H), 7.64 (t, $J_{HH} = 7.9$ Hz, 1H), 7.78 (t, $J_{HH} = 9.0$ Hz, 2H), 7.87–7.94 (m, 3H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 106.8 (q, $J_{CF} = 1.9$ Hz, CH_{pyr}), 119.7 (q, $J_{CF} = 269.1$ Hz, CF_3), 123.7 (q, $J_{CF} = 272.4$ Hz, $\text{CF}_{3\text{Ar}}$), 122.7 (q, $J_{CF} = 3.0$ Hz), 123.4, 125.9, 128.6, 128.8, 128.9, 129.8, 131.3, 131.9 (q, $J_{CF} = 33.5$ Hz, C- CF_3), 134.0 (q, $J_{CF} = 39.4$ Hz, C- CF_3), 139.6, 152.3. ^{19}F NMR (376.3 MHz, CDCl_3) δ -58.5 (3F, $\text{CF}_{3\text{pyr}}$), -63.8 (3F, $\text{CF}_{3\text{Ar}}$). HRMS (ESI-TOF) m/z $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{17}\text{H}_{10}\text{F}_6\text{N}_2^+$: 357.0821, found 357.0823.

4-(5-(Trifluoromethyl)-3-phenyl-1H-pyrazol-1-yl)benzonitrile (3n). White crystals, mp 85–86 °C (279 mg, 89% yield). ^1H NMR (400.1 MHz, CDCl_3) δ 7.17 (s, 1H, CH_{pyr}), 7.38–7.47 (m, 3H, Ph), 7.72 (d, $J_{HH} = 8.7$ Hz, 2H, 4- CNC_6H_4), 7.78 (d, $J_{HH} = 8.7$ Hz, 2H, 4- CNC_6H_4), 7.83–7.87 (m, 2H, Ph). ^{13}C NMR (100.6 MHz, CDCl_3) δ 107.6 (q, $J_{CF} = 2.2$ Hz, CH_{pyr}), 112.7, 117.7, 119.5 (q, $J_{CF} = 269.4$ Hz, CF_3), 125.5, 125.8, 128.8, 129.1, 131.0, 133.1, 133.7 (q, $J_{CF} = 39.8$ Hz, C- CF_3), 142.4, 152.6. ^{19}F NMR (376.3 MHz, CDCl_3) δ -58.2. IR (cm^{-1}) ν 2254 (CN), 1460, 1170, 1125. HRMS (ESI-TOF) m/z $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{17}\text{H}_{10}\text{F}_3\text{N}_3^+$: 314.0900, found 314.0902.

3-(5-(Trifluoromethyl)-3-phenyl-1H-pyrazol-1-yl)benzoic acid (3o). Pale brown powder, mp 138–140 °C (312 mg, 94% yield). ^1H NMR (400.1 MHz, CDCl_3) δ 7.13 (s, 1H, CH_{pyr}), 7.34–7.39 (m, 1H), 7.41–7.45 (m, 2H), 7.56–7.61 (m, 1H), 7.77 (d, $J_{HH} = 7.8$ Hz, 1H), 7.84–7.88 (m, 2H), 8.21 (d, $J_{HH} = 7.8$ Hz, 1H), 8.32 (s, 1H), 11.94 (br s, 1H, CO_2H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 106.4, 119.6 (q, $J_{CF} = 269.1$ Hz, CF_3), 125.8, 127.1, 128.7, 129.2, 130.0, 130.6, 131.3, 133.8 (q, $J_{CF} = 39.4$ Hz, C- CF_3), 139.2, 151.9, 169.1. ^{19}F NMR (376.3 MHz, CDCl_3) δ -58.6; HRMS (ESI-TOF) m/z $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{17}\text{H}_{11}\text{F}_3\text{N}_2\text{O}_2\text{Na}^+$: 355.0665, found 355.0658.

5-(Trifluoromethyl)-1-(2-isopropylphenyl)-3-phenyl-1H-pyrazole (3p). Pale yellow oil (277 mg, 84% yield). ^1H NMR (400.1 MHz, CDCl_3) δ 1.25 (br s, 6H, $\text{CH}(\text{CH}_3)_2$), 2.51–2.62 (m, 1H, $\text{CH}(\text{CH}_3)_2$), 7.15 (s, 1H, CH_{pyr}), 7.31–7.35 (m, 1H), 7.37–7.42 (m, 2H), 7.45–7.56 (m, 4H), 7.90–7.94 (m, 2H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 22.7 (br s.), 24.7 (br s.), 28.2, 104.7 (q, $J_{CF} = 1.8$ Hz, CH_{pyr}), 119.6 (q, $J_{CF} = 269.1$ Hz, CF_3), 125.5, 126.0, 126.6, 127.8, 128.5, 128.8, 130.6, 131.9, 134.8 (q, $J_{CF} = 38.7$ Hz, C- CF_3), 136.5, 147.0, 151.1. ^{19}F NMR (376.3 MHz, CDCl_3) δ -60.0. HRMS (ESI-TOF) m/z $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{19}\text{H}_{17}\text{F}_3\text{N}_2^+$: 331.1417, found 331.1418.

5-(Trifluoromethyl)-1-(2,4-dinitrophenyl)-3-phenyl-1H-pyrazole (3q). Yellow oil (268 mg, 71% yield). ^1H NMR (400.1 MHz, CDCl_3) δ 7.22 (s, 1H, CH_{pyr}), 7.37–7.45 (m, 3H, Ph), 7.74–7.77 (m, 2H, Ph),

7.89 (d, $J_{HH} = 8.7$ Hz, 1H), 8.62 (dd, $J_{HH} = 8.7$ Hz, $J_{HH} = 2.4$ Hz, 1H), 8.94 (d, $J_{HH} = 2.4$ Hz, 1H). ^{13}C NMR (100.6 MHz, CDCl_3) δ 107.6 (q, $J_{CF} = 1.9$ Hz, CH_{pyr}), 119.3 (q, $J_{CF} = 269.4$ Hz, CF_3), 121.3, 126.0, 127.8, 128.9, 129.5, 130.4, 130.5, 135.0 (q, $J_{CF} = 39.8$ Hz, C- CF_3), 136.9, 146.0, 147.9, 154.2. ^{19}F NMR (376.3 MHz, CDCl_3) δ -59.4. The NMR data are in agreement with previously reported.²²

4-[3-Phenyl-5-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide (3r). White powder, mp 201–203 °C (Lit. data²³ mp 199–201 °C) (312 mg, 85% yield). ^1H NMR (400.1 MHz, $\text{DMSO}-d_6$) δ 7.39–7.43 (m, 1H, Ph), 7.46–7.50 (m, 2H, Ph), 7.59 (s, 2H, NH_2), 7.78 (s, 1H, CH_{pyr}), 7.83 (d, $J_{HH} = 8.5$ Hz, 2H, 4-(SO_2NH_2) C_6H_4), 7.95 (d, $J_{HH} = 8.5$ Hz, 2H, 4-(SO_2NH_2) C_6H_4), 8.04 (d, $J_{HH} = 8.8$ Hz, 2H, Ph). ^{13}C NMR (100.6 MHz, $\text{DMSO}-d_6$) δ 107.7 (q, $J_{CF} = 1.9$ Hz, CH_{pyr}), 119.6 (q, $J_{CF} = 269.4$ Hz, CF_3), 125.7, 126.2, 127.0, 128.9, 129.0, 130.9, 132.9 (q, $J_{CF} = 38.7$ Hz, C- CF_3), 140.9, 144.9, 151.6. ^{19}F NMR (376.3 MHz, $\text{DMSO}-d_6$) δ -56.7. The NMR data are in agreement with previously reported.²³

5-(Trifluoromethyl)-1-(perfluorophenyl)-3-phenyl-1H-pyrazole (3s). Colorless crystals, mp 85–87 °C (344 mg, 91% yield). ^1H NMR (400.1 MHz, CDCl_3) δ 7.19 (s, 1H, CH_{pyr}), 7.39–7.48 (m, 3H, Ph), 7.82–7.85 (m, 2H, Ph). ^{13}C NMR (100.6 MHz, CDCl_3) δ 106.5 (q, $J_{CF} = 1.8$ Hz, CH_{pyr}), 114.2 (td, $J_{CF} = 13.6$ Hz, $J_{CF} = 4.4$ Hz, C_6F_6), 119.1 (q, $J_{CF} = 269.4$ Hz, CF_3), 126.0, 128.9, 129.3, 130.8, 136.2 (q, $J_{CF} = 40.2$ Hz, C- CF_3), 137.6 (dt, $J_{CF} = 252.8$ Hz, $J_{CF} = 13.3$ Hz, C_6F_6), 144.7 (ddt, $J_{CF} = 257.3$ Hz, $J_{CF} = 11.4$ Hz, $J_{CF} = 3.1$ Hz, C_6F_6), 154.2. ^{19}F NMR (376.3 MHz, CDCl_3) δ -62.0 (s, 3F, CF_3), -145.3 to -145.4 (m, 2F, C_6F_6), -150.0 to -150.1 (m, 1F, C_6F_6), -161.4 to -161.2 (m, 2F, C_6F_6). HRMS (ESI-TOF) m/z $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{16}\text{H}_7\text{F}_8\text{N}_2^+$: 379.0476, found 379.0476.

1-(2,6-Dichlorophenyl)-5-(trifluoromethyl)-3-phenyl-1H-pyrazole (3t). Pale yellow crystals, mp 94–96 °C (343 mg, 96% yield). ^1H NMR (400.1 MHz, CDCl_3) δ 7.17 (s, 1H, CH_{pyr}), 7.38–7.42 (m, 2H, Ph), 7.44–7.49 (m, 4H), 7.88–7.91 (m, 2H, Ph). ^{13}C NMR (100.6 MHz, CDCl_3) δ 105.5 (q, $J_{CF} = 1.8$ Hz, CH_{pyr}), 119.2 (q, $J_{CF} = 269.4$ Hz, CF_3), 126.0, 128.6, 128.8, 128.9, 131.5, 131.7, 134.8, 135.0 (q, $J_{CF} = 39.4$ Hz, C- CF_3), 135.6, 152.9. ^{19}F NMR (376.3 MHz, CDCl_3) δ -62.1. HRMS (ESI-TOF) m/z $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{16}\text{H}_6\text{Cl}_2\text{F}_3\text{N}_2^+$: 357.0168, found 357.0163.

1-tert-Butyl-5-(trifluoromethyl)-3-phenyl-1H-pyrazole (3v). Colorless oil (157 mg, 59% yield). ^1H NMR (400.1 MHz, CDCl_3) δ 1.72 (s, 9H), 7.00 (s, 1H), 7.31–7.35 (m, 1H, Ph), 7.40–7.43 (m, 2H, Ph), 7.81–7.83 (m, 2H, Ph). ^{19}F NMR (376.5 MHz, CDCl_3) δ -56.0. The NMR data are in agreement with previously reported.⁸

4-[3-(4-Methylphenyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide (3w). Pale yellow powder, mp 180–181 °C (350 mg, 92% yield). ^1H NMR (400.1 MHz, CDCl_3) δ 2.40 (s, 3H, Me), 5.13 (s, 2H, NH_2), 7.14 (s, 1H, CH_{pyr}), 7.26 (d, $J_{HH} = 8.0$ Hz, 2H, 4- MeC_6H_4), 7.74 (d, $J_{HH} = 8.8$ Hz, 2H, 4-(SO_2NH_2) C_6H_4), 7.76 (d, $J_{HH} = 8.0$ Hz, 2H, 4- MeC_6H_4), 8.07 (d, $J_{HH} = 8.8$ Hz, 2H, 4-(SO_2NH_2) C_6H_4). ^{13}C NMR (100.6 MHz, CDCl_3) δ 21.3, 107.9 (q, $J_{CF} = 2.2$ Hz, CH_{pyr}), 119.6 (q, $J_{CF} = 269.4$ Hz, CF_3), 125.7, 125.8, 127.6, 128.3, 129.6, 133.8 (q, $J_{CF} = 39.4$ Hz, C- CF_3), 139.1, 142.2, 142.5, 152.6. ^{19}F NMR (282.4 MHz, CDCl_3) δ -58.4. The NMR data are in agreement with previously reported.⁸

1-(4-Chlorophenyl)-5-(trifluoromethyl)-3-(4-methoxyphenyl)-1H-pyrazole (3x). Pale yellow crystals, mp 79–81 °C (282 mg, 80% yield). ^1H NMR (400.1 MHz, CDCl_3) δ 3.86 (s, 3H, MeO), 6.96 (d, $J_{HH} = 8.8$ Hz, 2H, 4- MeOC_6H_4), 7.03 (s, 1H, CH_{pyr}), 7.46 (d, $J_{HH} = 9.0$ Hz, 2H, 4- ClC_6H_4), 7.50 (d, $J_{HH} = 9.0$ Hz, 2H, 4- ClC_6H_4), 7.77 (d, $J_{HH} = 8.8$ Hz, 2H, 4- MeOC_6H_4). ^{13}C NMR (100.6 MHz, CDCl_3) δ 55.3, 106.0 (q, $J_{CF} = 2.2$ Hz, CH_{pyr}), 114.2, 119.6 (q, $J_{CF} = 269.4$ Hz, CF_3), 124.2, 126.8, 127.1, 129.3, 133.7 (q, $J_{CF} = 39.1$ Hz, C- CF_3), 135.1, 137.7, 151.8, 160.2. ^{19}F NMR (376.3 MHz, CDCl_3) δ -58.7. HRMS (ESI-TOF) m/z $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{17}\text{H}_{12}\text{ClF}_3\text{N}_2\text{O}^+$: 353.0663, found 353.0665.

3-(4-Chlorophenyl)-5-(trifluoromethyl)-1-(4-methoxyphenyl)-1H-pyrazole (3y). Pale yellow-orange crystals, mp 105–107 °C (212 mg, 60% yield). ^1H NMR (400.1 MHz, CDCl_3) δ 3.84 (s, 3H, MeO), 6.96 (d, $J_{HH} = 8.9$ Hz, 2H, 4- MeOC_6H_4), 7.04 (s, 1H, CH_{pyr}), 7.39 (d, J_{HH}

= 8.4 Hz, 2H, 4-ClC₆H₄), 7.44 (d, J_{HH} = 8.9 Hz, 2H, 4-MeOC₆H₄), 7.78 (d, J_{HH} = 9.0 Hz, 2H, 4-ClC₆H₄). ¹³C NMR (100.6 MHz, CDCl₃) δ 55.5, 105.5 (q, J_{CF} = 1.8 Hz, CH_{pyr}), 114.2, 119.6 (q, J_{CF} = 269.1 Hz, CF₃), 127.0, 127.2, 129.0, 130.3, 131.9, 134.2 (q, J_{CF} = 39.1 Hz, C-CF₃), 134.4, 150.2, 160.2. ¹⁹F NMR (376.3 MHz, CDCl₃) δ -59.1. HRMS (ESI-TOF) m/z [M + H]⁺ Calcd for C₁₇H₁₂ClF₃N₂O⁺: 353.0663, found 353.0644.

Synthesis of Pyrazoles 4 by the Reaction of Ketones 1 with Hydrazines 2 in HFIP (General Procedure I). A 3 mL screw neck vial was charged with HFIP (2 mL), corresponding ketone 1 (1 mmol), aryl hydrazine 2* (1.05 mmol) and maintained for 1 day at room temperature. HFIP was evaporated in vacuo, the residue was purified by column chromatography on silica gel using appropriate mixtures of hexane and CH₂Cl₂ (2:1–1:1, 4a–m, p–u, s–w, SC-500), CH₂Cl₂ (4n), or mixture of CH₂Cl₂ and MeOH (30:1, 4o, 4r). Aryl hydrazine was generated in situ by mixing of equivalent amounts of aryl hydrazine hydrochloride and DBU.

Synthesis of Pyrazoles 4 by the Reaction of Ketones 1 with Hydrazines Hydrochlorides 2 in DMSO (General Procedure II). A 3 mL screw neck vial was charged with DMSO (2 mL), corresponding ketone 1 (1 mmol), hydrochloride of aryl hydrazine 2 (1.05 mmol) and maintained for 1 day at room temperature. Next, DBU (304 mg, 2 mmol) was added and reaction mixture was left for 1 day. After that reaction mixture was poured into ~0.1 M solution of HCl (50 mL), extracted with CH₂Cl₂ (3 × 20 mL). The combined organic phase was washed with water (50 mL), dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography on silica gel using appropriate mixtures of hexane and CH₂Cl₂ (2:1–1:1, 4a, b, f, g, j, k, m, s, x, y, z and 4aa), CH₂Cl₂ (4n), or mixture of CH₂Cl₂ and MeOH (30:1, 4o, 4r, Celebrex).

3-(Trifluoromethyl)-1,5-diphenyl-1H-pyrazole (4a). Light yellow powder (282 mg, 98% yield (I)); 271 mg, 94% yield (II)). The characterization data (mp and NMR) are given in previous section.

5-(4-Chlorophenyl)-3-(trifluoromethyl)-1-phenyl-1H-pyrazole (4b). Pale yellow oil (319 mg, 99% yield (I)); 233 mg, 72% yield (II)). ¹H NMR (600.2 MHz, CDCl₃) δ 6.75 (s, 1H, CH_{pyr}), 7.15 (d, J_{HH} = 8.4 Hz, 2H, 4-ClC₆H₄), 7.28–7.31 (m, 4H), 7.35–7.39 (m, 3H). ¹³C NMR (150.9 MHz, CDCl₃) δ 105.6 (q, J_{CF} = 2.2 Hz, CH_{pyr}), 121.2 (q, J_{CF} = 269.6 Hz, CF₃), 125.4, 127.5, 128.6, 128.9, 129.2, 129.9, 135.1, 138.9, 143.2 (q, J_{CF} = 38.5 Hz, C-CF₃), 143.4. ¹⁹F NMR (564.7 MHz, CDCl₃) δ -63.2. The NMR data are in agreement with previously reported.^{4c}

5-(4-Bromophenyl)-3-(trifluoromethyl)-1-phenyl-1H-pyrazole (4c). Pale yellow crystals, mp 104–106 °C (363 mg, 99% yield (I)). ¹H NMR (600.2 MHz, CDCl₃) δ 6.75 (s, 1H, CH_{pyr}), 7.09 (d, J_{HH} = 8.4 Hz, 2H, 4-BrC₆H₄), 7.27–7.32 (m, 2H, Ph), 7.35–7.39 (m, 3H, Ph), 7.45 (d, J_{HH} = 8.4 Hz, 2H, 4-BrC₆H₄). ¹³C NMR (150.9 MHz, CDCl₃) δ 105.6 (q, J_{CF} = 2.2 Hz, CH_{pyr}), 121.1 (q, J_{CF} = 268.5 Hz, CF₃), 123.4, 125.4, 128.0, 128.6, 129.2, 130.2, 131.9, 138.9, 143.2 (q, J_{CF} = 38.5 Hz, C-CF₃), 143.4. ¹⁹F NMR (564.6 MHz, CDCl₃) δ -63.3. The NMR data are in agreement with previously reported.²⁴

3-(Trifluoromethyl)-1-phenyl-5-p-tolyl-1H-pyrazole (4d). Pale yellow oil (284 mg, 94% yield (I)). ¹H NMR (600.2 MHz, CDCl₃) δ 2.35 (s, 3H, Me), 6.73 (s, 1H, CH_{pyr}), 7.11 (d, J_{HH} = 8.3 Hz, 2H, 4-MeC₆H₄), 7.13 (d, J_{HH} = 8.3 Hz, 2H, 4-MeC₆H₄), 7.31–7.34 (m, 2H, Ph), 7.35–7.38 (m, 3H, Ph). ¹³C NMR (150.9 MHz, CDCl₃) δ 21.2, 105.2 (q, J_{CF} = 2.2 Hz, CH_{pyr}), 121.3 (q, J_{CF} = 268.5 Hz, CF₃), 125.4, 126.2, 128.3, 128.6, 129.0, 129.3, 139.0, 139.3, 143.1 (q, J_{CF} = 38.5 Hz, C-CF₃), 144.8. ¹⁹F NMR (564.6 MHz, CDCl₃) δ -63.3. The NMR data are in agreement with previously reported.^{4c}

5-(4-tert-Butyl-phenyl)-1-phenyl-3-trifluoromethyl-1H-pyrazole (4e). Light brown solid, mp 107–108 °C (334 mg, 97% yield (I)). ¹H NMR (400 MHz, CDCl₃) δ 1.32 (s, 9H, *t*-Bu), 6.74 (s, 1H, C⁴H); 7.15–7.40 (m, 9H, Ar). ¹³C NMR (100.6 MHz, CDCl₃) δ 31.3 ((CH₃)₃), 34.8 (C⁶), 105.5 (C⁴), 121.5 (q, J = 269 Hz, CF₃), 125.7, 125.8, 125.9, 126.3, 128.5, 129.2, 139.5 (Ar, Ph); 143.2 (q, J = 38 Hz, C³); 144.9 (C⁵), 152.4 (C⁷). ¹⁹F NMR (376.5 MHz, CDCl₃) δ -62.4. ¹⁵N NMR (40.6 MHz, CDCl₃) δ -165.1, -74.4. IR (KBr, cm⁻¹) ν 1132, 1161 (C–F), 1596, 1620 (C=C, C=N). Anal. Calcd for

C₂₀H₁₉F₃N₂: C 69.75; H 5.56; N 8.13. Found: C 69.89; H 5.52; N 8.43.

3-(Trifluoromethyl)-5-(4-methoxyphenyl)-1-phenyl-1H-pyrazole (4f). Pale yellow oil (308 mg, 97% yield (I)); 273 mg, 86% yield (II)). ¹H NMR (600.2 MHz, CDCl₃) δ 3.78 (s, 3H, MeO), 6.70 (s, 1H, CH_{pyr}), 6.83 (d, J_{HH} = 8.4 Hz, 2H, 4-MeOC₆H₄), 7.14 (d, J_{HH} = 8.4 Hz, 2H, 4-MeOC₆H₄), 7.30–7.33 (m, 2H, Ph), 7.33–7.37 (m, 3H, Ph). ¹³C NMR (150.9 MHz, CDCl₃) δ 55.1, 104.9 (q, J_{CF} = 2.2 Hz, CH_{pyr}), 114.0, 121.3, 121.4 (q, J_{CF} = 268.5 Hz, CF₃), 125.4, 128.3, 129.0, 130.0, 139.3, 143.0 (q, J_{CF} = 38.5 Hz, C-CF₃), 144.5, 160.0. ¹⁹F NMR (564.7 MHz, CDCl₃) δ -63.2. The NMR data are in agreement with previously reported.^{4c}

3-(Trifluoromethyl)-5-(4-(methylthio)phenyl)-1-phenyl-1H-pyrazole (4g). Pale yellow crystals, mp 77–80 °C (304 mg, 91% yield (I)); 267 mg, 80% yield (II)). ¹H NMR (600.2 MHz, CDCl₃) δ 2.44 (s, 3H, MeS), 6.73 (s, 1H, CH_{pyr}), 7.12 (d, J_{HH} = 8.4 Hz, 2H, 4-MeSC₆H₄), 7.13 (d, J_{HH} = 8.4 Hz, 2H, 4-MeSC₆H₄), 7.30–7.33 (m, 2H, Ph), 7.34–7.37 (m, 3H, Ph). ¹³C NMR (150.9 MHz, CDCl₃) δ 14.8, 105.2 (q, J_{CF} = 2.2 Hz, CH_{pyr}), 121.2 (q, J_{CF} = 268.5 Hz, CF₃), 125.2, 125.4, 125.7, 128.4, 128.9, 129.0, 139.1, 140.3, 143.0 (q, J_{CF} = 38.5 Hz, C-CF₃), 144.1. ¹⁹F NMR (564.7 MHz, CDCl₃) δ -63.2. HRMS (ESI-TOF) m/z [M + H]⁺ Calcd for C₁₇H₁₄F₃N₂S⁺: 335.0824, found 335.0819.

3-(Trifluoromethyl)-5-(1-methoxynaphthalen-4-yl)-1-phenyl-1H-pyrazole (4h). White powder, mp 91–93 °C (367 mg, 100% yield (I)). ¹H NMR (400.1 MHz, CDCl₃) δ 4.02 (s, 3H, MeO), 6.77 (d, J_{HH} = 8.0 Hz, 1H), 6.83 (s, 1H, CH_{pyr}), 7.18–7.21 (m, 3H), 7.24–7.28 (m, 3H), 7.46–7.53 (m, 2H), 7.69–7.72 (m, 1H), 8.34–8.36 (m, 1H). ¹³C NMR (100.6 MHz, CDCl₃) δ 55.5, 103.1, 107.6 (q, J_{CF} = 1.1 Hz, CH_{pyr}), 119.0, 121.4 (q, J_{CF} = 268.7 Hz, CF₃), 122.4, 124.2, 124.7, 125.5, 125.7, 127.5, 127.8, 128.8, 129.4, 132.6, 139.3, 142.8, 143.0 (q, J_{CF} = 38.3 Hz, C-CF₃), 156.5. ¹⁹F NMR (376.3 MHz, CDCl₃) δ -63.1. HRMS (ESI-TOF) m/z [M + H]⁺ Calcd for C₂₁H₁₆F₃N₂O⁺: 369.1209, found 369.1205.

3-(Trifluoromethyl)-5-(2,3-dihydrobenzo[*b*][1,4]dioxin-7-yl)-1-phenyl-1H-pyrazole (4i). Pale yellow crystals, mp 122–124 °C (342 mg, 99% yield (I)). ¹H NMR (400.1 MHz, CDCl₃) δ 4.19–4.25 (m, 4H, -OCH₂CH₂O-), 6.63 (dd, J_{HH} = 8.4 Hz, 2.2 Hz, 1H), 6.67 (s, 1H, CH_{pyr}), 6.76–6.78 (m, 2H), 7.31–7.39 (m, 5H, Ph). ¹³C NMR (100.6 MHz, CDCl₃) δ 64.2, 64.3, 105.1 (q, J_{CF} = 1.1 Hz, CH_{pyr}), 117.5, 117.7, 121.3 (q, J_{CF} = 268.7 Hz, CF₃), 122.0, 122.2, 125.4, 128.4, 129.0, 139.2, 142.9 (q, J_{CF} = 38.3 Hz, C-CF₃), 143.5, 144.3. ¹⁹F NMR (376.3 MHz, CDCl₃) δ -63.3. HRMS (ESI-TOF) m/z [M + H]⁺ Calcd for C₁₈H₁₄F₃N₂O₂⁺: 347.1002, found 347.1002.

5-Hexyl-1-phenyl-3-trifluoromethyl-1H-pyrazole (4j). Light yellow oil (278 mg, 94% yield (I)); 234 mg, 79% yield (II)). ¹H NMR (400 MHz, CDCl₃) δ 0.80–0.90 (m, 3H, CH₃), 1.20–1.35 (m, 6H, CH₂), 1.50–1.65 (m, 2H, CH₂), 2.61 (t, J = 7.8 Hz, 2H, CH₂), 6.45 (s, 1H, C⁴H), 7.35–7.55 (m, 5H, Ph). ¹³C NMR (100.6 MHz, CDCl₃) δ 14.1, 22.6, 26.3, 28.7, 28.9, 31.5 (Hex), 103.6 (q, J = 2 Hz, C⁴), 122.8 (q, J = 269 Hz, CF₃), 125.9, 129.0, 129.4, 139.2 (Ph), 142.9 (q, J = 38 Hz, C³), 146.0 (C⁵). ¹⁹F NMR (376.5 MHz, CDCl₃) δ -62.5. IR (KBr, cm⁻¹) ν 1134, 1179 (C–F), 1559, 1599 (C=C, C=N). Anal. Calcd for C₁₆H₁₉F₃N₂: C 64.85; H 6.46; N 9.45. Found: C 64.79; H 6.80; N 9.39. MS (EI), m/z (%) 296 (17, M⁺), 239 (52), 226 (100). The NMR data are in agreement previously reported.²¹

1-(4-Bromophenyl)-3-(trifluoromethyl)-5-phenyl-1H-pyrazole (4k). White powder, mp 73–74 °C (301 mg, 82% yield (I)); 253 mg, 69% yield (II)). ¹H NMR (400.1 MHz, CDCl₃) δ 6.74 (s, 1H, CH_{pyr}), 7.17–7.23 (m, 4H), 7.32–7.40 (m, 3H), 7.48 (d, J_{HH} = 8.8 Hz, 2H, 4-BrC₆H₄). ¹³C NMR (100.6 MHz, CDCl₃) δ 105.9 (q, J_{CF} = 1.2 Hz, CH_{pyr}), 121.1 (q, J_{CF} = 269.4 Hz, CF₃), 122.2, 126.8, 128.8, 128.9, 129.2, 132.2, 138.2, 143.5 (q, J_{CF} = 38.3 Hz, C-CF₃), 144.7. ¹⁹F NMR (376.3 MHz, CDCl₃) δ -63.5. HRMS (ESI-TOF) m/z [M + H]⁺ Calcd for C₁₆H₁₁BrF₃N₂⁺: 367.0058, found 367.0054.

3-(Trifluoromethyl)-5-phenyl-1-p-tolyl-1H-pyrazole (4l). Pale yellow crystals, mp 86–88 °C (278 mg, 92% yield (I)). ¹H NMR (400.1 MHz, CDCl₃) δ 2.36 (s, 3H, Me), 6.73 (s, 1H, CH_{pyr}), 7.13–7.23 (m, 6H), 7.29–7.36 (m, 3H). ¹³C NMR (100.6 MHz, CDCl₃) δ 21.1, 105.3 (q, J_{CF} = 1.6 Hz, CH_{pyr}), 121.3 (q, J_{CF} = 269.1 Hz, CF₃), 125.3,

128.6, 128.8, 128.9, 129.3, 129.6, 136.8, 138.5, 143.0 (q, $J_{CF} = 38.3$ Hz, C-CF₃), 144.5. ¹⁹F NMR (376.3 MHz, CDCl₃) δ -63.3. HRMS (ESI-TOF) m/z [M + H]⁺ Calcd for C₁₇H₁₄F₃N₂⁺: 303.1104, found 303.1103.

3-(Trifluoromethyl)-1-(3-(trifluoromethyl)phenyl)-5-phenyl-1H-pyrazole (4m). Pale yellow crystals, mp 66–68 °C (295 mg, 83% yield (I); 256 mg, 72% yield (II)). ¹H NMR (400.1 MHz, CDCl₃) δ 6.78 (s, 1H, CH_{pyr}), 7.20–7.24 (m, 2H), 7.33–7.42 (m, 3H), 7.44–7.48 (m, 2H), 7.59–7.63 (m, 1H), 7.64 (s, 1H). ¹³C NMR (100.6 MHz, CDCl₃) δ 106.2, 121.1 (q, $J_{CF} = 269.1$ Hz, CF₃pyr), 122.3 (q, $J_{CF} = 4.1$ Hz), 123.3 (q, $J_{CF} = 272.8$ Hz, CF₃Ar), 125.0 (q, $J_{CF} = 3.7$ Hz), 128.4, 128.7, 128.8, 128.9, 129.4, 129.7, 131.7 (q, $J_{CF} = 33.5$ Hz, C-CF₃), 139.6, 143.9 (q, $J_{CF} = 38.7$ Hz, C-CF₃), 145.0. ¹⁹F NMR (376.3 MHz, CDCl₃) δ -63.5 (3F, CF₃pyr), -64.0 (3F, CF₃Ar). HRMS (ESI-TOF) m/z [M + H]⁺ Calcd for C₁₇H₁₀F₆N₂⁺: 357.0821, found 357.0815.

4-(3-(Trifluoromethyl)-5-phenyl-1H-pyrazol-1-yl)benzotrile (4n). Pale yellow crystals, mp 88–90 °C (216 mg, 69% yield (I); 219 mg, 70% yield (II)). ¹H NMR (400.1 MHz, CDCl₃) δ 6.77 (s, 1H, CH_{pyr}), 7.20–7.24 (m, 2H, Ph), 7.36–7.41 (m, 3H, Ph), 7.44 (d, $J_{HH} = 8.6$ Hz, 2H, 4-CNC₆H₄), 7.63 (d, $J_{HH} = 8.6$ Hz, 2H, 4-CNC₆H₄). ¹³C NMR (100.6 MHz, CDCl₃) δ 106.7 (q, $J_{CF} = 1.6$ Hz, CH_{pyr}), 111.9, 117.8, 120.9 (q, $J_{CF} = 269.4$ Hz, CF₃), 125.4, 128.5, 128.8, 129.0, 129.6, 133.0, 142.4, 144.2 (q, $J_{CF} = 38.7$ Hz, C-CF₃), 145.0. ¹⁹F NMR (376.3 MHz, CDCl₃) δ -63.6. The NMR data are in agreement with previously reported.²⁵

3-(3-(Trifluoromethyl)-5-phenyl-1H-pyrazol-1-yl)benzoic acid (4o). Pale brown crystals, mp 159–162 °C (302 mg, 91% yield (I); 329 mg, 99% yield (II)). ¹H NMR (400.1 MHz, CDCl₃) δ 6.78 (s, 1H, CH_{pyr}), 7.20–7.24 (m, 2H, Ph), 7.31–7.36 (m, 3H, Ph), 7.44 (d, $J_{HH} = 7.8$ Hz, 1H), 7.50 (dd, $J_{HH} = 7.8$ Hz, $J_{HH} = 1.6$ Hz, 1H), 8.08 (d, $J_{HH} = 7.8$ Hz, 1H), 8.11 (d, $J_{HH} = 1.6$ Hz, 1H), 12.02 (br s, 1H, CO₂H). ¹³C NMR (100.6 MHz, CDCl₃) δ 105.8, 121.1 (q, $J_{CF} = 268.7$ Hz, CF₃), 126.9, 128.6, 128.7, 128.8, 129.2, 129.9, 130.2, 130.7, 139.4, 143.5 (q, $J_{CF} = 38.3$ Hz, C-CF₃), 144.9, 170.3. ¹⁹F NMR (376.3 MHz, CDCl₃) δ -63.3. IR (cm⁻¹) ν 1700 (C=O). HRMS (ESI-TOF) m/z [M - H + 2Na]⁺ Calcd for C₁₇H₁₀F₃N₂O₂Na₂⁺: 377.0484, found 377.0494.

3-(Trifluoromethyl)-1-(2-isopropylphenyl)-5-phenyl-1H-pyrazole (4p). Pale yellow oil (297 mg, 90% yield (I)). ¹H NMR (400.1 MHz, CDCl₃) δ 0.90 (br s, 3H, CH(CH₃)₂), 1.04 (br s, 3H, CH(CH₃)₂), 2.53 (sept, 1H, $J_{HH} = 6.9$ Hz, CH(CH₃)₂), 6.83 (s, 1H, CH_{pyr}), 7.17–7.21 (m, 2H), 7.23–7.31 (m, 5H), 7.37 (d, $J_{HH} = 7.4$ Hz, 1H), 7.45 (td, $J_{HH} = 7.4$ Hz, $J_{HH} = 2.0$ Hz, 1H). ¹³C NMR (100.6 MHz, CDCl₃) δ 22.0–24.9 (m, CH(CH₃)₂), 28.0 (CH(CH₃)₂), 103.8, 121.3 (q, $J_{CF} = 268.7$ Hz, CF₃), 126.5, 126.9, 128.1, 128.2, 128.6, 128.8, 130.1, 137.2, 142.8 (q, $J_{CF} = 38.3$ Hz, C-CF₃), 145.8, 145.9. ¹⁹F NMR (376.3 MHz, CDCl₃) δ -63.2. HRMS (ESI-TOF) m/z [M + H]⁺ Calcd for C₁₉H₁₇F₃N₂⁺: 331.1417, found 331.1417.

3-(Trifluoromethyl)-1-(2,4-dinitrophenyl)-5-phenyl-1H-pyrazole (4q). Pale yellow oil (19 mg, 5% yield (I)). ¹H NMR (400.1 MHz, CDCl₃) δ 6.83 (s, 1H, CH_{pyr}), 7.17–7.22 (m, 2H, Ph), 7.34–7.44 (m, 3H, Ph), 7.61 (d, $J_{HH} = 8.7$ Hz, 1H, 2,4-diNO₂C₆H₄), 8.45 (dd, $J_{HH} = 8.7$, $J_{HH} = 2.4$ Hz, 1H, 2,4-(NO₂)₂C₆H₄), 8.77 (d, $J_{HH} = 2.4$ Hz, 1H, 2,4-(NO₂)₂C₆H₄). ¹³C NMR (100.6 MHz, CDCl₃) δ 106.3, 120.6 (q, $J_{CF} = 269.4$ Hz, CF₃), 121.1, 127.2, 127.7, 128.7, 129.3, 130.1, 130.7, 137.2, 143.6, 145.7 (q, $J_{CF} = 38.3$ Hz, C-CF₃), 146.6, 147.2. ¹⁹F NMR (376.3 MHz, CDCl₃) δ -63.8. HRMS (ESI-TOF) m/z [M + H]⁺ Calcd for C₁₆H₁₀F₃N₄O₄⁺: 379.0649, found 379.0649.

4-[5-Phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (4r). White powder, mp 160–162 °C (125 mg, 34% yield (I); 297 mg, 81% yield (II)). ¹H NMR (400.1 MHz, CDCl₃) δ 5.46 (s, 2H, NH₂), 6.76 (s, 1H, CH_{pyr}), 7.21 (dd, $J_{HH} = 7.8$ Hz, $J_{HH} = 1.7$ Hz, 2H, Ph), 7.31–7.38 (m, 3H, Ph), 7.40 (d, $J_{HH} = 8.6$ Hz, 2H, 4-(SO₂NH₂)C₆H₄), 7.84 (d, $J_{HH} = 8.6$ Hz, 2H, 4-(SO₂NH₂)C₆H₄). ¹³C NMR (100.6 MHz, CDCl₃) δ 109.4, 117.7, 119.6 (q, $J_{CF} = 269.4$ Hz, CF₃), 125.7, 126.2, 127.0, 128.9, 129.0, 130.9, 132.9 (q, $J_{CF} = 38.7$ Hz, C-CF₃), 140.9, 144.9, 151.6. ¹⁹F NMR (376.3 MHz, CDCl₃) δ -63.6. The NMR data are in agreement with previously reported.⁸

3-(Trifluoromethyl)-1-(perfluorophenyl)-5-phenyl-1H-pyrazole (4s). Pale yellow crystals, mp 79–81 °C (8 mg, 2% yield (I); 249 mg,

66% yield (II)). ¹H NMR (400.1 MHz, CDCl₃) δ 6.84 (s, 1H, CH_{pyr}), 7.24–7.28 (m, 2H, Ph), 7.32–7.47 (m, 3H, Ph). ¹³C NMR (100.6 MHz, CDCl₃) δ 105.1, 114.7–115.0 (m, C₆F₆), 120.7 (q, $J_{CF} = 269.4$ Hz, CF₃), 127.9, 128.9, 129.1, 130.1, 137.7 (dtd, $J_{CF} = 259.1$ Hz, $J_{CF} = 12.5$ Hz, $J_{CF} = 5.2$ Hz, C₆F₆), 142.4 (dt, $J_{CF} = 246.2$ Hz, $J_{CF} = 13.3$ Hz, C₆F₆), 143.9 (ddt, $J_{CF} = 256.9$ Hz, $J_{CF} = 7.8$ Hz, $J_{CF} = 3.9$ Hz, C₆F₆), 145.8 (q, $J_{CF} = 39.1$ Hz, C-CF₃), 148.4. ¹⁹F NMR (376.3 MHz, CDCl₃) δ -63.9 (s, 3F, CF₃), -145.2 to -145.4 (m, 2F, C₆F₆), -150.7 to -150.9 (m, 1F, C₆F₆), -161.0 to -161.2 (m, 2F, C₆F₆). HRMS (ESI-TOF) m/z [M + H]⁺ Calcd for C₁₆H₆F₈N₂⁺: 379.0476, found 379.0469.

3-(Trifluoromethyl)-1-(2,4-dimethylphenyl)-5-phenyl-1H-pyrazole (4t). Slight yellow solid, mp 92–93 °C (284 mg, 90% yield (I); 285 mg, 90% yield (II)). ¹H NMR (400.1 MHz, CDCl₃) δ 1.92 (s, 3H, CH₃), 2.36 (s, 3H, CH₃), 6.80 (s, 1H, CH_{pyr}), 7.03–7.07 (m, 2H, Ar), 7.15–7.21 (m, 3H, Ar), 7.25–7.33 (m, 3H, Ar); ¹³C NMR (100.6 MHz, CDCl₃) δ 17.3 (CH₃), 21.4 (CH₃), 103.8 (q, $J_{CF} = 1.5$ Hz, C⁴), 121.3 (q, $J_{CF} = 268.3$ Hz, CF₃), 127.4, 127.6, 127.9, 128.6, 128.7, 129.0, 131.7, 134.9, 136.1, 139.6, 142.8 (q, $J_{CF} = 38.0$ Hz, C-CF₃), 145.6. ¹⁹F NMR (CDCl₃) δ -63.3. IR (film, cm⁻¹) 1132, 1163 (C-F), 1569, 1608, 1614 (C=C, C=N, Ph). Anal. Calcd for C₁₈H₁₅F₃N₂: C 68.35; H 4.78; N 8.86. Found: C 68.26; H 4.83; N 8.74. MS (EI), m/z (%) 316 (100, M⁺), 301 (33), 247 (21), 239 (13), 220 (14), 77 (16).

1-(4-Chlorophenyl)-3-(trifluoromethyl)-5-phenyl-1H-pyrazole (4u). Orange solid, mp 77–78 °C (235 mg, 73% yield (I)). ¹H NMR (400.1 MHz, CDCl₃) δ 6.77 (s, 1H, C⁴H), 7.20–7.50 (m, 9H, Ar). ¹³C NMR (100.6 MHz, CDCl₃) δ 106.1 (C⁴), 121.4 (q, $J_{CF} = 269.0$ Hz, CF₃), 126.7, 129.0, 129.0, 129.4, 129.4, 134.1, 134.5 (Ar), 137.9 (C⁵), 143.7 (q, $J_{CF} = 38.3$ Hz, C³), 145.0 (Ar). ¹⁹F NMR (376.5 MHz, CDCl₃) δ -62.6. IR (film, cm⁻¹) ν 1135, 1163 (C-F), 1572, 1596, 1650 (C=C, C=N, Ph). Anal. Calcd for C₁₆H₁₀ClF₃N₂: C 59.55; H 3.12; N 8.68. Found: C 59.33; H 3.18; N 8.42.

3-(Trifluoromethyl)-1-(4-methoxyphenyl)-5-phenyl-1H-pyrazole (4v). Light yellow solid, mp 78–79 °C (238 mg, 75% yield (I)). ¹H NMR (400.1 MHz, CDCl₃) δ 3.83 (s, 3H, OCH₃), 6.76 (s, 1H, C⁴H), 6.80–6.95 (m, 2H, Ar), 7.20–7.40 (m, 7H, Ar). ¹³C NMR (100.6 MHz, CDCl₃) δ 55.6 (OCH₃), 105.3 (C⁴), 121.6 (q, $J_{CF} = 269.0$ Hz, CF₃), 114.4, 127.0, 128.8, 128.9, 129.0, 129.4 (Ar), 132.6 (C⁵), 143.0 (q, $J_{CF} = 38.3$ Hz, C³), 144.8, 159.7 (Ar). ¹⁹F NMR (376.5 MHz, CDCl₃) δ -62.4. IR (film, cm⁻¹) ν 1132, 1162 (C-F), 1569, 1589, 1610 (C=C, C=N, Ph). Anal. Calcd for C₁₇H₁₃F₃N₂O: C 64.15; H 4.12; N 8.80. Found: C 63.96; H 4.11; N 8.87. MS (EI), m/z (%) 318 (100, M⁺), 303 (12), 297 (14), 275 (10), 77 (11). The NMR data are in agreement with previously reported.⁸

1-Ethyl-5-phenyl-3-trifluoromethyl-1H-pyrazole (4w). Maize yellow oil (228 mg, 95% yield (I); 116 mg, 48% yield (II)). ¹H NMR (400 MHz, CDCl₃) δ 1.41 (t, $J = 7$ Hz, 3H), 4.18 (q, $J = 7$ Hz, 2H), 6.50 (s, 1H), 7.35–7.55 (m, 5H, Ph); δ 1.52 (t, $J_{HH} = 7$ Hz, 3H), 4.30 (q, $J_{HH} = 7$ Hz, 2H), 6.84 (s, 1H), 7.30–7.85 (m, 5H, Ph). ¹³C NMR (100.6 MHz, CDCl₃) δ 15.7 (CH₃), 45.4 (CH₂), 104.5 (C⁴), 121.7 (q, $J_{CF} = 268$ Hz, CF₃), 129.1, 129.1, 129.4, 129.7 (Ph), 141.7 (q, $J_{CF} = 38$ Hz, C³), 144.7 (C⁵). ¹⁹F NMR (376.5 MHz, CDCl₃) δ -62.3. IR (film, cm⁻¹) ν 1128, 1167 (C-F), 1506, 1608 (C=C, C=N). Anal. Calcd for C₁₂H₁₁F₃N₂: C 60.00; H 4.62; N 11.66. Found: C 60.39; H 4.30; N 11.54. MS (EI), m/z (%) 240 (76, M⁺), 212 (100), 205 (18), 164 (18), 143 (17).

1-tert-Butyl-3-(trifluoromethyl)-5-phenyl-1H-pyrazole (4x). Colorless solid, mp 92–94 °C (117 mg, 44% yield (I); 132 mg, 49% yield (II)). ¹H NMR (400 MHz, CDCl₃) δ 1.46 (s, 9H), 6.38 (s, 1H), 7.32–7.35 (m, 2H, Ph), 7.38–7.46 (m, 3H, Ph); ¹³C NMR (100.6 MHz, CDCl₃) δ 30.9 (CH₃), 62.7 (C(CH₃)₃), 107.3 (C⁴), 121.6 (q, $J_{CF} = 268.3$ Hz, CF₃), 128.0, 129.0, 130.4, 132.7 (Ph), 139.2 (q, $J_{CF} = 37.6$ Hz, C³), 144.0 (C⁵). ¹⁹F NMR (376.5 MHz, CDCl₃) δ -62.9. The NMR data are in agreement with previously reported.⁸

1-(2,6-Dichlorophenyl)-3-(trifluoromethyl)-5-phenyl-1H-pyrazole (4y). Colorless crystals, mp 62–64 °C (296 mg, 83% yield (II)). ¹H NMR (400.1 MHz, CDCl₃) δ 6.82 (s, 1H, CH_{pyr}), 7.26–7.41 (m, 8H, Ph). ¹³C NMR (100.6 MHz, CDCl₃) δ 104.2 (q, $J_{CF} = 1.5$ Hz, CH_{pyr}), 121.1 (q, $J_{CF} = 269.4$ Hz, CF₃), 127.8, 128.3, 128.7, 129.4, 131.4, 135.1, 135.2, 144.5 (q, $J_{CF} = 38.7$ Hz, C-CF₃), 147.2. ¹⁹F NMR (376.3

MHz, CDCl₃) δ -63.5. HRMS (ESI-TOF) m/z [M + H]⁺ Calcd for C₁₆H₉Cl₃F₃N₃⁺: 357.0168, found 357.0161.

bis(4-(3-(Trifluoromethyl)-5-phenyl-1H-pyrazol-1-yl)phenyl)methane (4z). Pale yellow powder, mp 138–139 °C (395 mg, 67% yield (II)). ¹H NMR (400.1 MHz, CDCl₃) δ 4.01 (s, 2H, CH₂), 6.75 (s, 2H, CH_{pyr}), 7.15 (d, J_{HH} = 8.3 Hz, 4H), 7.22–7.28 (m, 8H, Ph), 7.30–7.39 (m, 6H, Ph). ¹³C NMR (100.6 MHz, CDCl₃) δ 40.9, 105.5 (q, J_{CF} = 1.1 Hz, CH_{pyr}), 121.3 (q, J_{CF} = 269.1 Hz, CF₃), 125.6, 128.7, 128.8, 129.0, 129.2, 129.6, 137.6, 140.8, 143.1 (q, J_{CF} = 38.3 Hz, C-CF₃), 144.6. ¹⁹F NMR (376.3 MHz, CDCl₃) δ -63.4. HRMS (ESI-TOF) m/z [M + Na]⁺ Calcd for C₃₃H₂₂F₆N₄Na⁺: 611.1641, found 611.1629.

4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (Celebrex). Pale yellow powder, mp 160–161 °C (Lit. data²³ mp 160–162 °C) (328 mg, 86% yield (II)). ¹H NMR (400.1 MHz, CDCl₃) δ 2.33 (s, 3H, Me), 5.53 (s, 2H, NH₂), 6.72 (s, 1H, CH_{pyr}), 7.08 (d, J_{HH} = 8.2 Hz, 2H, 4-MeC₆H₄), 7.15 (d, J_{HH} = 8.2 Hz, 2H, 4-MeC₆H₄), 7.40 (d, J_{HH} = 8.6 Hz, 2H, 4-(SO₂NH₂)C₆H₄), 7.84 (d, J_{HH} = 8.6 Hz, 2H, 4-(SO₂NH₂)C₆H₄). ¹H NMR (400.1 MHz, DMSO-*d*₆) δ 2.31 (s, 3H, Me), 6.97 (s, 1H, CH_{pyr}), 7.15 (d, J_{HH} = 8.4 Hz, 2H, 4-MeC₆H₄), 7.18 (d, J_{HH} = 8.4 Hz, 2H, 4-MeC₆H₄), 7.40 (s, 2H, NH₂), 7.46 (d, J_{HH} = 8.8 Hz, 2H, 4-(SO₂NH₂)C₆H₄), 7.86 (d, J_{HH} = 8.8 Hz, 2H, 4-(SO₂NH₂)C₆H₄). ¹³C NMR (100.6 MHz, DMSO-*d*₆) δ 20.7, 105.8, 121.0 (q, J_{CF} = 268.7 Hz, CF₃), 125.2, 125.3, 126.6, 128.5, 129.2, 138.9, 140.9, 142.3 (q, J_{CF} = 38.0 Hz, C-CF₃), 143.8, 144.9. ¹⁹F NMR (376.3 MHz, DMSO-*d*₆) δ -62.3. ¹⁹F NMR (376.3 MHz, CDCl₃) δ -63.6. The NMR data are in agreement with previously reported.⁸

1-(4-Chlorophenyl)-3-(trifluoromethyl)-5-(4-methoxyphenyl)-1H-pyrazole (4aa). Pale yellow oil (352 mg, 100% yield (I)); 314 mg, 89% yield (II)). ¹H NMR (400.1 MHz, CDCl₃) δ 3.82 (s, 3H, MeO), 6.70 (s, 1H, CH_{pyr}), 6.88 (d, J_{HH} = 8.8 Hz, 2H, 4-MeOC₆H₄), 7.15 (d, J_{HH} = 8.8 Hz, 2H, 4-MeOC₆H₄), 7.27 (d, J_{HH} = 8.8 Hz, 2H, 4-ClC₆H₄), 7.34 (d, J_{HH} = 8.8 Hz, 2H, 4-ClC₆H₄). ¹³C NMR (100.6 MHz, CDCl₃) δ 55.2, 105.3 (q, J_{CF} = 1.5 Hz, CH_{pyr}), 114.2, 121.1, 121.2 (q, J_{CF} = 269.1 Hz, CF₃), 126.5, 129.2, 130.1, 134.1, 137.8, 143.3 (q, J_{CF} = 38.3 Hz, C-CF₃), 144.6, 160.2. ¹⁹F NMR (376.3 MHz, CDCl₃) δ -63.4. The NMR data are in agreement with previously reported.^{12a}

5-(4-Chlorophenyl)-3-(trifluoromethyl)-1-(4-methoxyphenyl)-1H-pyrazole (SC-560). Yellow oil (321 mg, 91% yield (I)); 280 mg, 79% yield (II)). ¹H NMR (400.1 MHz, CDCl₃) δ 3.81 (s, 3H, MeO), 6.72 (s, 1H, CH_{pyr}), 6.87 (d, J_{HH} = 8.8 Hz, 2H, 4-MeOC₆H₄), 7.14 (d, J_{HH} = 8.5 Hz, 2H, 4-ClC₆H₄), 7.20 (d, J_{HH} = 8.8 Hz, 2H, 4-MeOC₆H₄), 7.29 (d, J_{HH} = 8.5 Hz, 2H, 4-ClC₆H₄). ¹³C NMR (100.6 MHz, CDCl₃) δ 55.5, 105.2, 114.3, 121.2 (q, J_{CF} = 269.1 Hz, CF₃), 126.8, 127.6, 128.9, 129.9, 132.0, 135.0, 142.9 (q, J_{CF} = 38.3 Hz, C-CF₃), 143.4, 159.6. ¹⁹F NMR (376.3 MHz, CDCl₃) δ -63.3. The NMR data are in agreement with previously reported.^{13b}

(2-(1,1,1-Trifluoro-4-phenylbut-3-yn-2-ylidene)-1-(2,4-dinitrophenyl)hydrazine (7b). Obtained as an admixture in the reaction of 2,4-dinitrophenylhydrazine with ketone **1a** in HFIP. Yellow-orange powder, mp 183–185 °C (45 mg, 12% yield). ¹H NMR (400.1 MHz, CDCl₃) δ 7.44–7.54 (m, 3H, Ph), 7.72–7.75 (m, 2H, Ph), 8.06 (d, J_{HH} = 9.4 Hz, 1H, 2,4-diNO₂C₆H₃), 8.43 (dd, J_{HH} = 9.4 Hz, J_{HH} = 2.4 Hz, 1H, 2,4-(NO₂)₂C₆H₄), 9.16 (d, J_{HH} = 2.4 Hz, 1H, 2,4-(NO₂)₂C₆H₄), 12.11 (br s, 1H, NH). ¹³C NMR (100.6 MHz, CDCl₃) δ 74.8, 109.4, 117.7, 119.2, 119.3 (q, J_{CF} = 272.8 Hz, CF₃), 123.0, 125.6 (q, J_{CF} = 39.4 Hz, C-CF₃), 129.0, 130.3, 131.4, 132.7, 140.5, 143.1. ¹⁹F NMR (376.3 MHz, CDCl₃) δ -68.4. IR (cm⁻¹) ν 1342, 1470, 1520, 1620, 2215. HRMS (ESI-TOF) m/z [M - H]⁺ Calcd for C₁₆H₈F₃N₄O₄⁺: 377.0503, found 377.0502.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00774.

¹H, ¹³C, and ¹⁹F NMR spectra of all compounds and quantum chemical calculations data (PDF)

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Notes

The authors declare no competing financial interest.

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