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Article

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Selective, Metal-free Approach to 3- or 5-CF_3-Pyrazoles. Solvent Switchable Reaction of CF_3-ynones with Hydrazines

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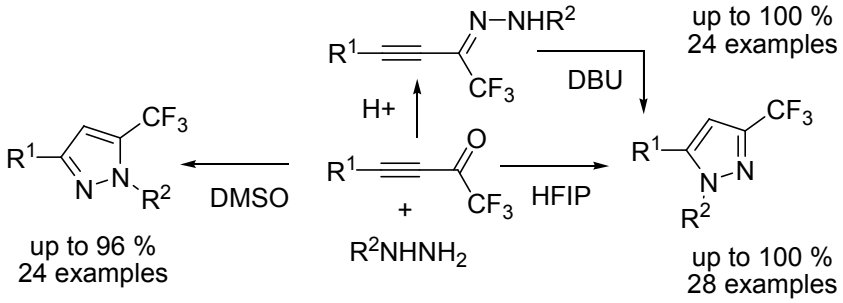


Abstract

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-CF_3-substituted isomers was preferentially observed. Alternatively, the regioselective assembly of 3-CF_3-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-CF_3-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 type 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 CF_3-substituted pyrazoles.[4]

In the recent years many approaches towards trifluoromethylated pyrazoles were developed. The modern metodologies for the synthesis of pyrazoles bearing fluorine or fluorine-containing functional group at various position of this heterocyclic molecule were analysed very recently.[4d] Generally, CF_3-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 CF_3-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 CF_3-pyrazoles is still a significant challenge of modern organic synthesis. Very recently, the preferential formation of either 3- or 5-CF_3-pyrazoles from ynones and arylhydrazines 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 CF_3-ynones and alkyl- and arylhydrazines and the study of the reaction mechanism.

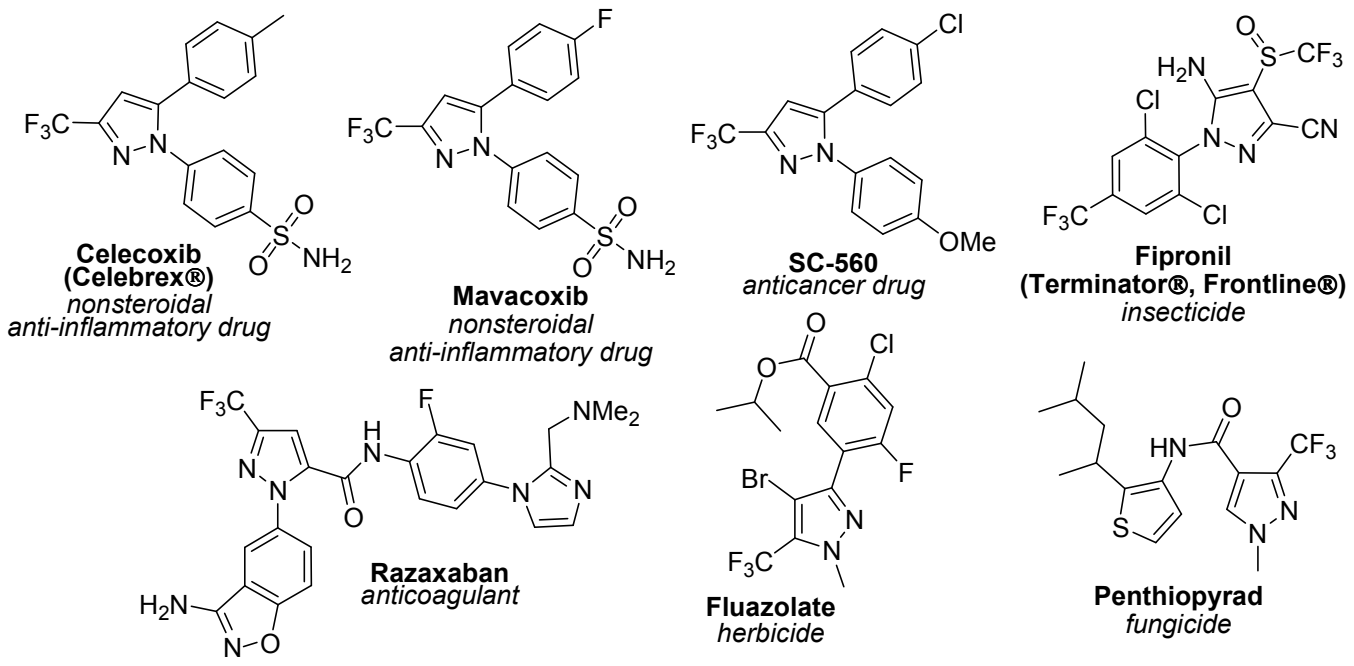


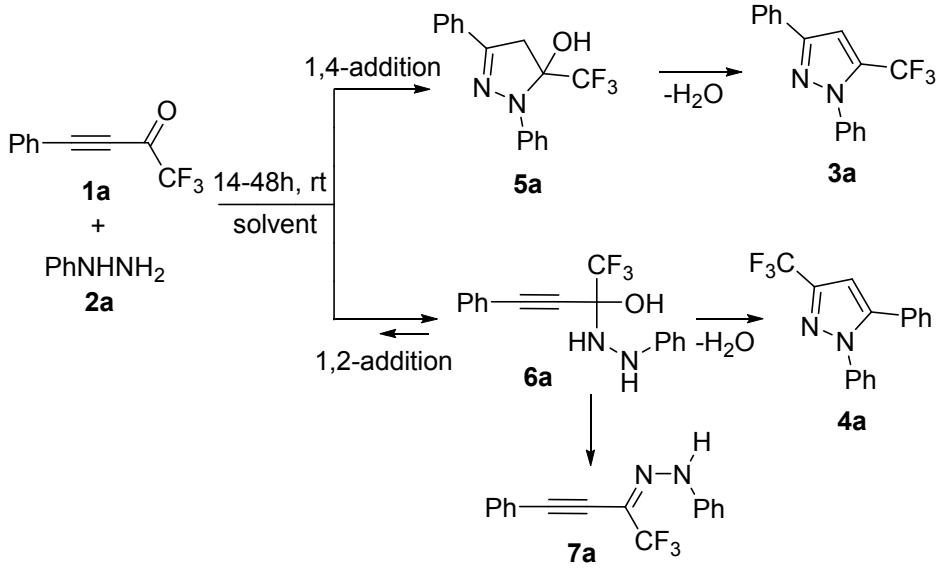
Figure 1. Some examples of bioactive CF_3-pyrazoles.

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 ^{19}F NMR. It was found 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 ^{1}H, ^{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.



Scheme 1. Reaction of ynone **1a** with phenylhydrazine **2a** in different solvents.

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	$Me_2N(CH_2)_2OH$	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)

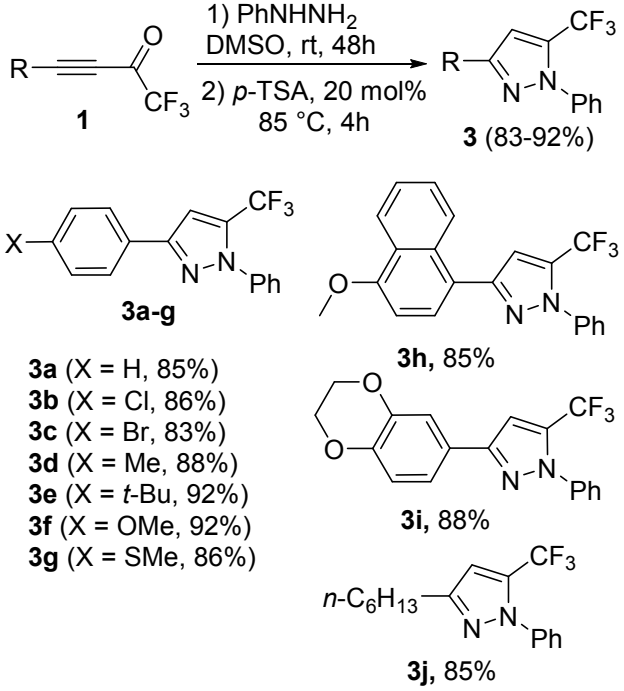
13	*t*-BuOH	19	67	12	0	2
14	$HO(CH_2)_2OH$	0(13)	87(87)	13(13)	0(0)	0(0)
15	MeOH	0(20)	80(80)	20(0)	0(0)	0(0)
16	EtOH	12	88	0	0	0
17	**HFIP**	**2**	**98**	**0**	**0**	**0**
18	AcOH	3	30	0	0	67
19	$THF+BF_3 \cdot Et_2O$	0	3	0	0	97

[a] - yields obtained after heating of the reaction mixture with *p*-TSA are given in parentheses. [b]- composition of the reaction mixture after 14h / 48h.

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 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 non-toxic solvent for further research due to its simpler work up procedures and NMR reaction control. More basic solvents such as Et_3N and $Me_2N(CH_2)_2OH$ afforded preferentially **5a**. In contrast, the reaction in non-polar medium (hexane, toluene, $CHCl_3$) and polar protic solvents (fluorinated and non-fluorinated alcohols) resulted in 3-CF_3-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 ($BF_3 \cdot Et_2O$ 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-CF_3-pyrazole **3a**, whereas 3-CF_3-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-CF_3-pyrazoles or 5-CF_3-pyrazoles) by a proper choice of the solvent was demonstrated.

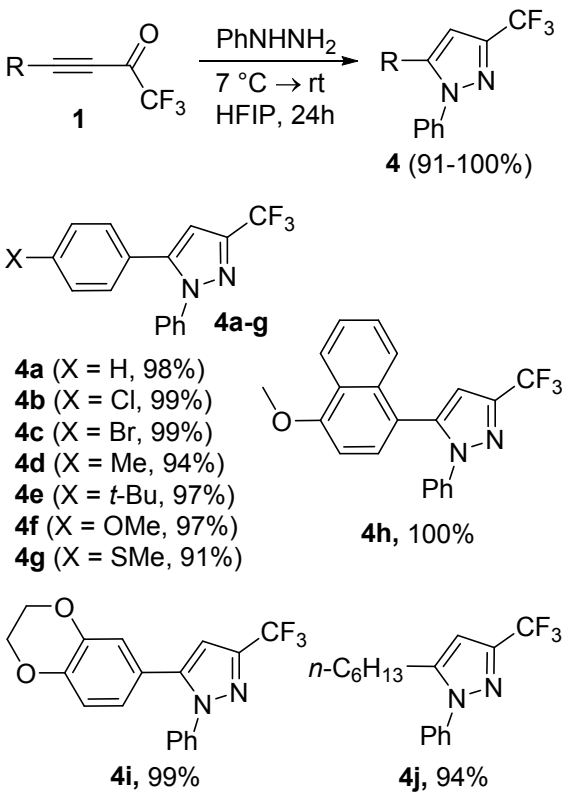
Having in hand the optimal reaction conditions for the selective formation of each isomer, the synthetic scope of the reaction was studied. A number of ynones bearing both aryl and alkyl substituents at the triple bond was treated with phenylhydrazine in DMSO for two days at room temperature followed by heating at 85°C with p-TSA for 4h. As a result, a number of 5-CF_3 pyrazoles **3a-j** was prepared in high isolated yields (Scheme 2).



Scheme 2. Scope of the reaction of ynones **1** with phenylhydrazine to form 5-CF_3-pyrazoles **3**.

The reaction of ketones **1a-j** with phenylhydrazine in HFIP showed even better results to give isomeric 3-CF_3-pyrazoles **4a-j** in excellent yield and regioselectivity. It should be noted 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-CF_3-pyrazoles **4**.

The configuration of isomeric pyrazoles **3j** and **4j** with aliphatic substituent was determined on the basis of the concerted application of $^{1}H - {}^{1}H$ 2D homonuclear experiment NOESY and $^{1}H - {}^{13}C$ 2D heteronuclear experiment HMBC (Figure 2). Thus, intensive cross peaks between the resonance signals of the $C^{5}CH_2$ 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 ^{19}F NMR spectra.[5,6f]

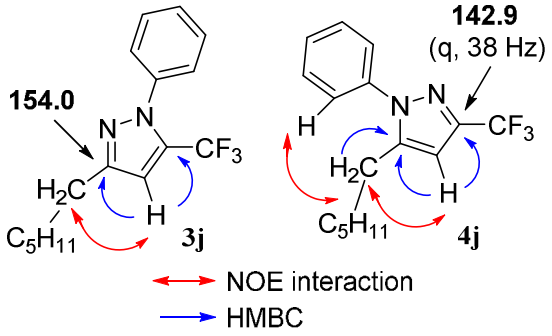
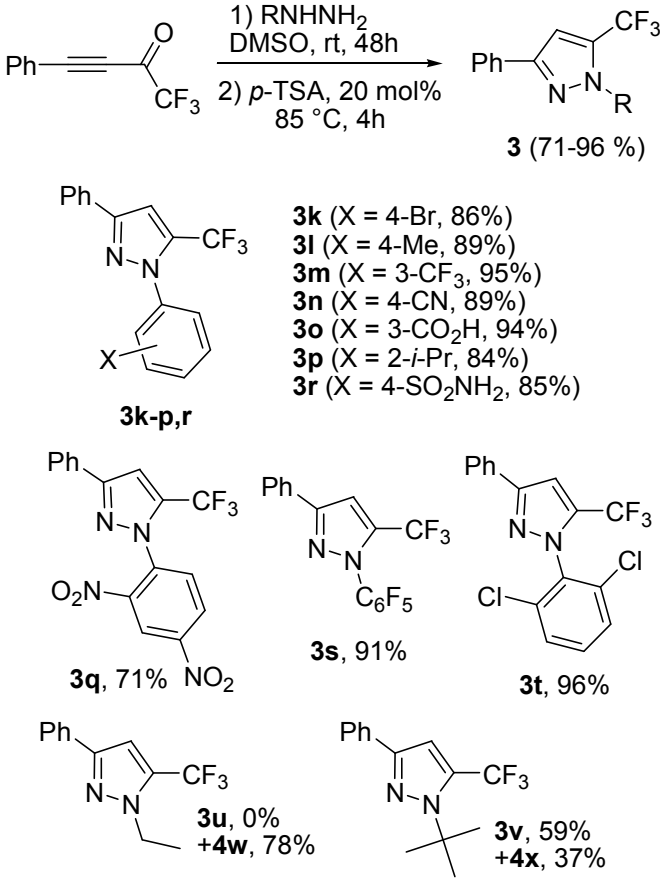


Figure 2. Main NOESY and HMBC correlations for pyrazoles **3j** and **4j**.

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 variety of substituents (*ortho*-isopropyl, 2,6-dichloro, pentafluoro) and functional groups (CO_2H, SO_2NH_2, 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-CF_3-pyrazole **3u** at all to form only 3-CF_3-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.

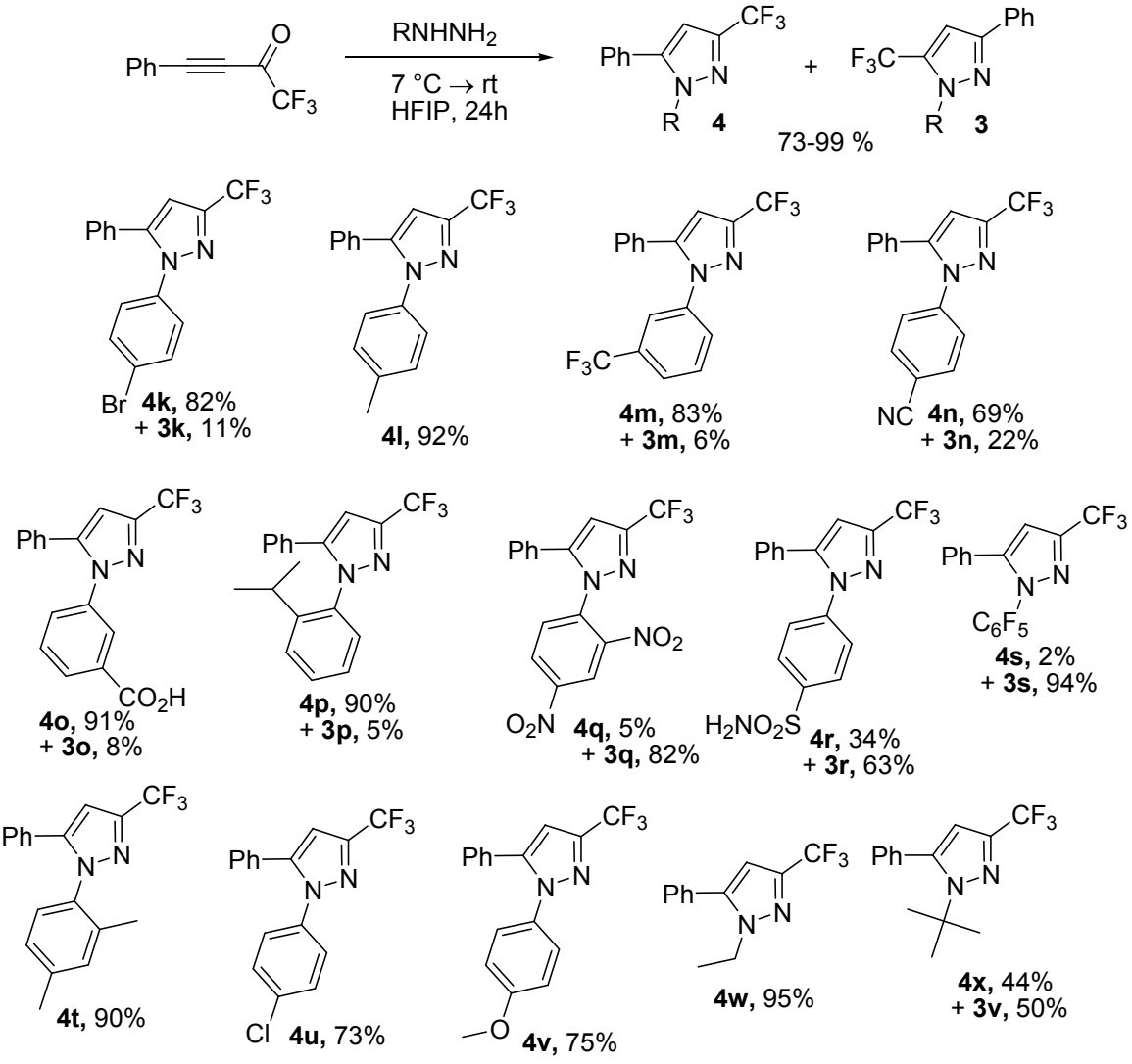


Scheme 4. Scope of the reaction of **1a** with various hydrazines **2** to form 5-CF_3-pyrazoles.

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-CF_3-pyrazoles **4** highly regioselectively (Scheme 5). To our delight, the reaction with highly nucleophilic ethylhydrazine afforded regioselectively 3-CF_3-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 regiosomeric 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-CF_3-pyrazole **3** fraction in the mixture of CF_3-pyrazole products. Moreover, in the case of highly electron-poor 2,4-dinitrophenyl-, 4-aminosulfonylphenyl-, and polyfluorophenylhydrazine the corresponding 5-CF_3-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

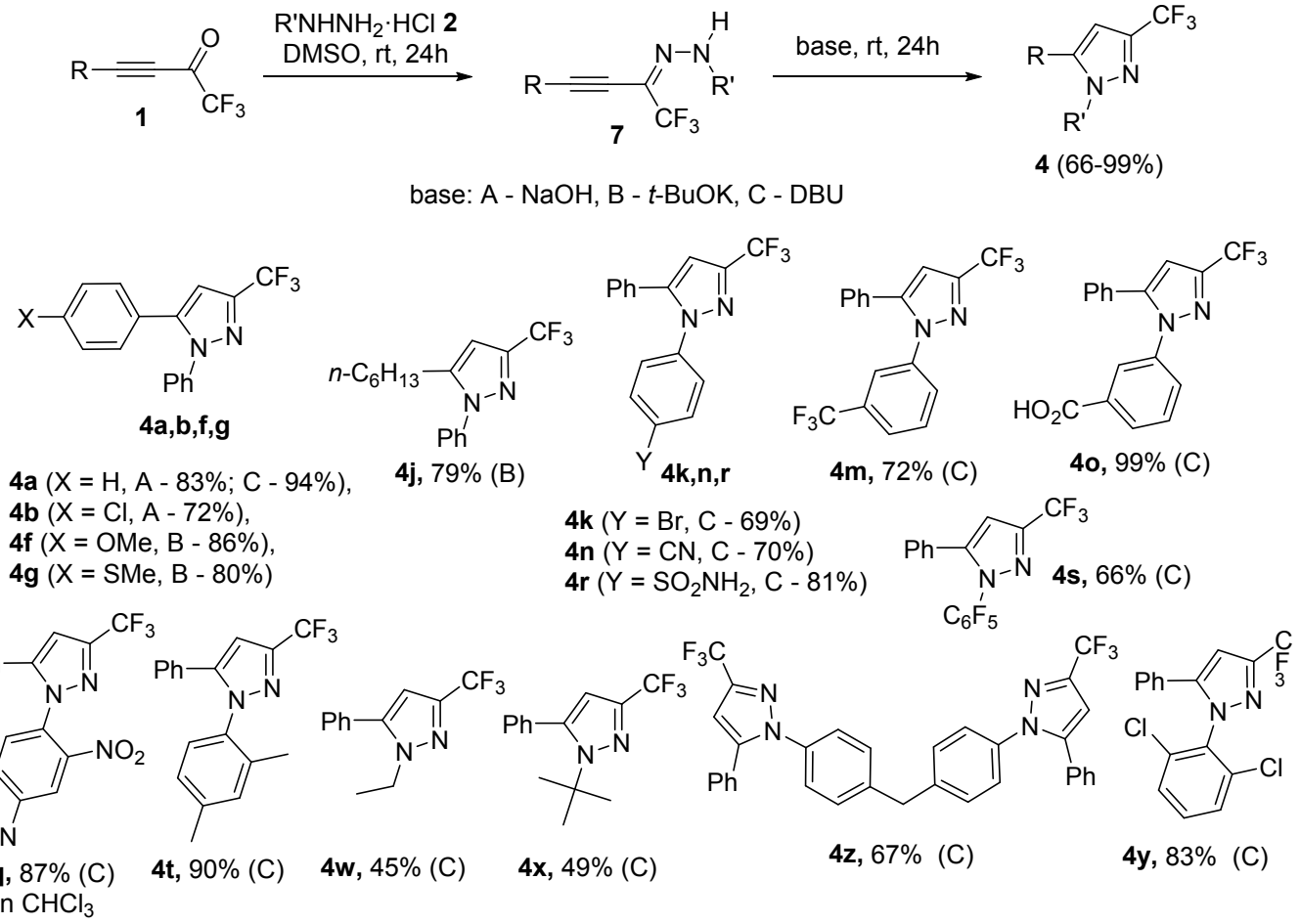
12%) and only 4% and 2% of pyrazoles **4q,s** (Scheme 5). Therefore, this approach was found to be most applicable for the selective preparation of 3-CF_3-pyrazoles **4** with the highly nucleophilic aryl and alkyl hydrazines. The reaction has the significant restrictions in terms of regioselectivity 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 CF_3-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]



Scheme 5. Scope of the reaction of **1a** with various hydrazines to form 3-CF_3-pyrazoles **4**.

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). It has been reported that acetylenic hydrazones can be transformed into pyrazoles by the treatment with a base[4c,10] or by the transition metals[11] catalysis. Taking 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.



Scheme 6. Synthesis of 3-CF_3-pyrazoles **4** *via* intermediate formation of hydrazones.

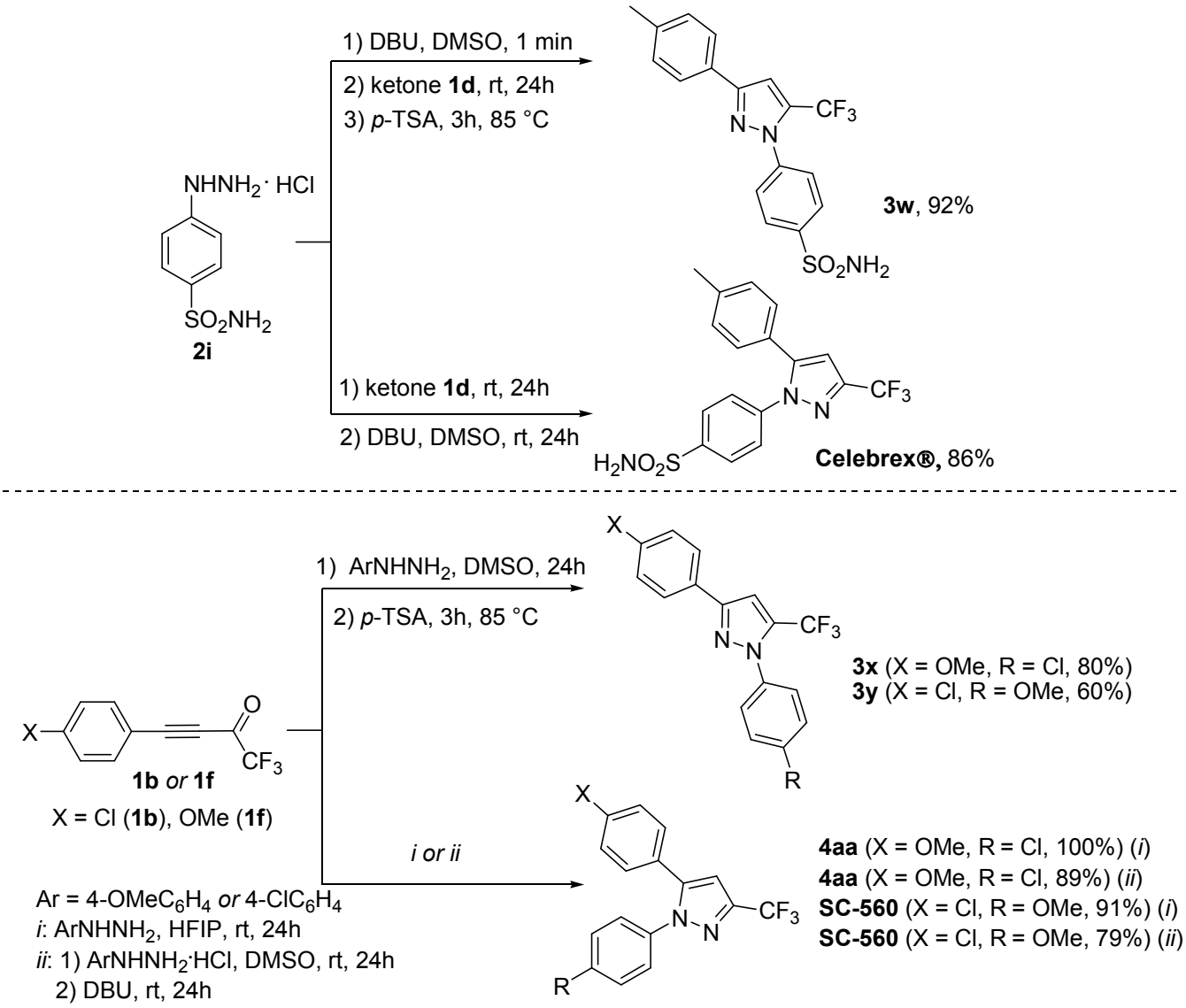
Hydrazones **7** were easily prepared *in situ* by the reaction of ketones **1** with aryl hydrazine hydrochlorides **2**·HCl in DMSO at room temperature; their formation was confirmed by ^{19}F NMR spectroscopy. Next, different reaction conditions were examined for the cyclization of intermediate hydrazones. It was found that this reaction proceeds efficiently in the presence of the strong inorganic (NaOH) or organic (*t*-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 5M 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 **Celebrex** 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, **Celebrex** 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,4c,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).



Scheme 7. Synthesis of **Celebrex**, **SC-560**, and their regioisomers

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.

To get a clue 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 one minute at rt. The structure of **6b** was elucidated by analysis of both NMR and IR spectra. Only two singlets of *tert*-butyl group (the initial ynone **1** and new compound in the ratio 1:3) were presented in the ^{1}H 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 C≡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.

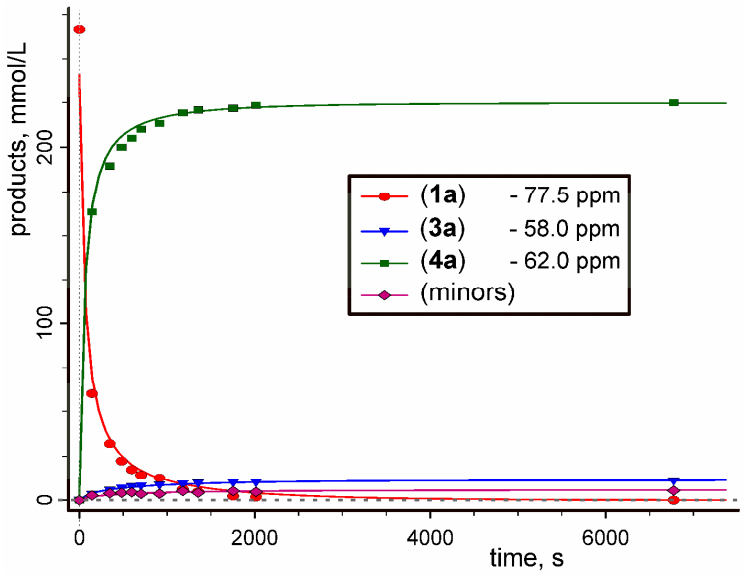


Figure 3. Monitoring of the reaction of ynone **1a** with phenylhydrazine in HFIP.

The structure of **5b** was assigned by the comparison of its ^{19}F and ^{1}H NMR spectra with those of pyrazoline **5a**. The most characteristic signals in ^{1}H 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}H – ^{13}C HMBC and ^{1}H – ^{15}N HMBC). Thus, for structure **6b** correlations in 2D ^{1}H-^{15}N HMBC spectra allowed to assign the signals of H_o 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 ^{1}H NMR spectra (4.52 ppm) belongs to the second NH proton and has the coupling constant ^{1}J(H,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}H-^{13}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 (C=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.

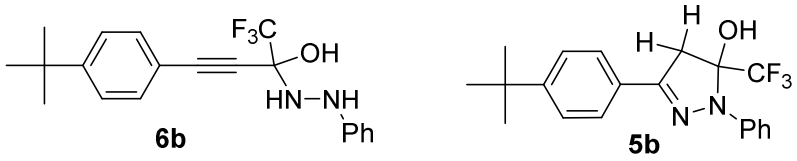


Figure 4. Structures of intermediates **5b** and **6b**.

The reaction of ynone **1a** with phenylhydrazine in 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 2h 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).

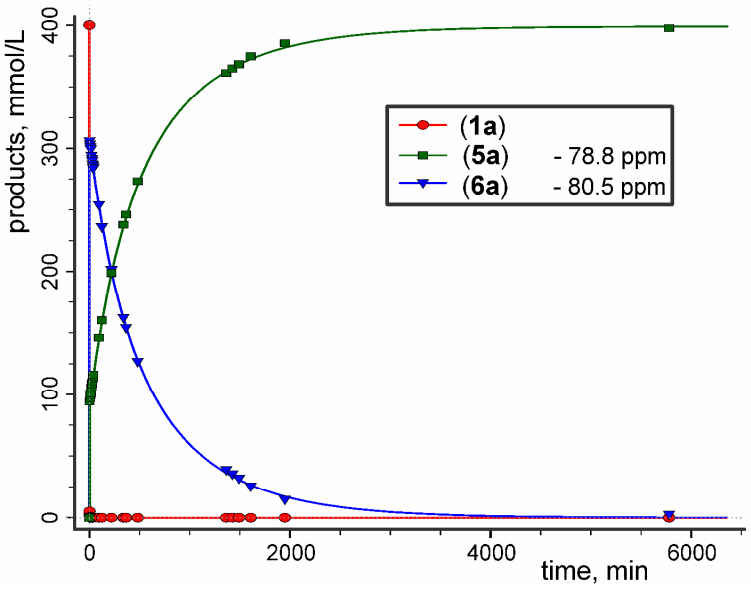
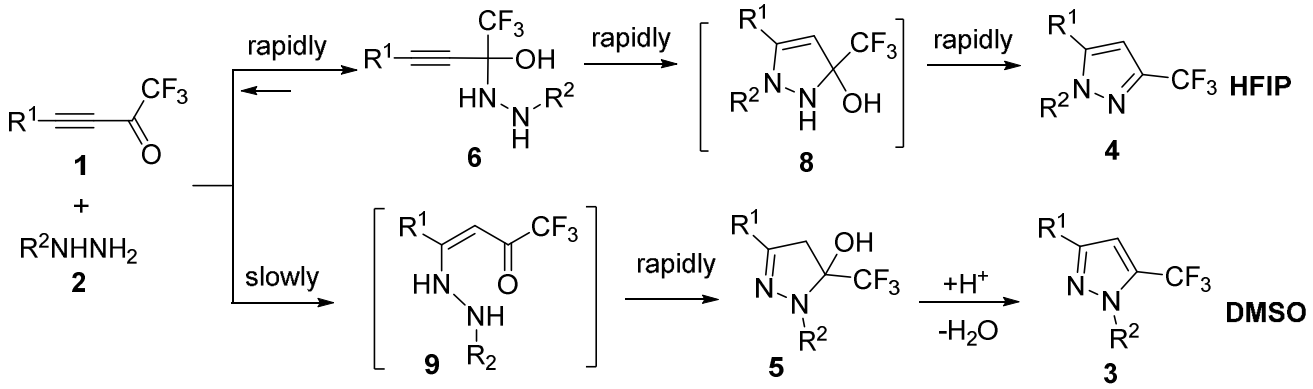


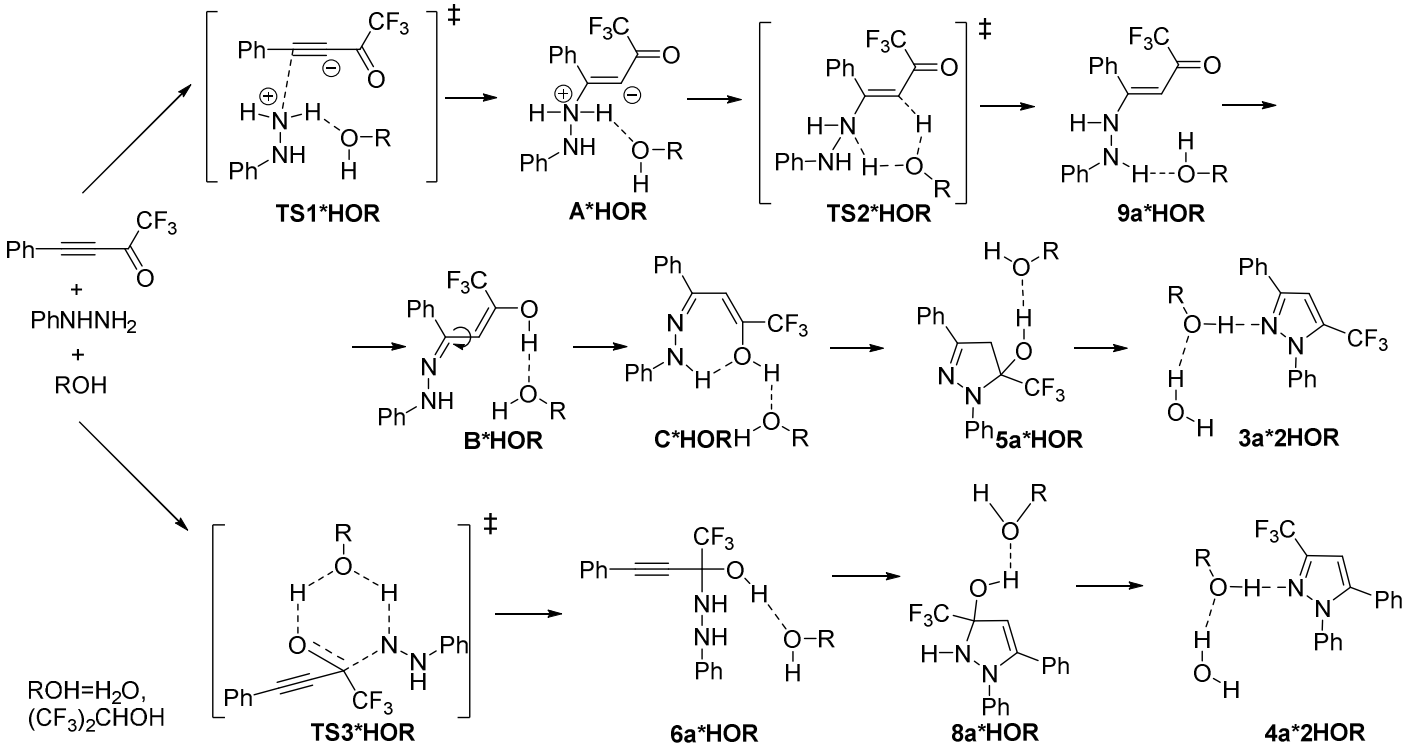
Figure 5. Monitoring of the reaction of **1a** with phenylhydrazine in DMSO-d_6.

The following scheme of the reaction can be proposed on the base 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 herein). 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.



Scheme 8. Possible mechanism of the reaction.

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).



Scheme 9. Probable reaction pathways in DMSO (ROH=H_2O) and HFIP (ROH=HFIP).

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 (**TS1*H_2O**) is 6.7 kcal/mol lower than the addition energy to the carbonyl group (**TS3*H_2O**), 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 significant difference of the corresponding transition states for the competitive processes (**TS1*HFIP)** and (**TS3*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.

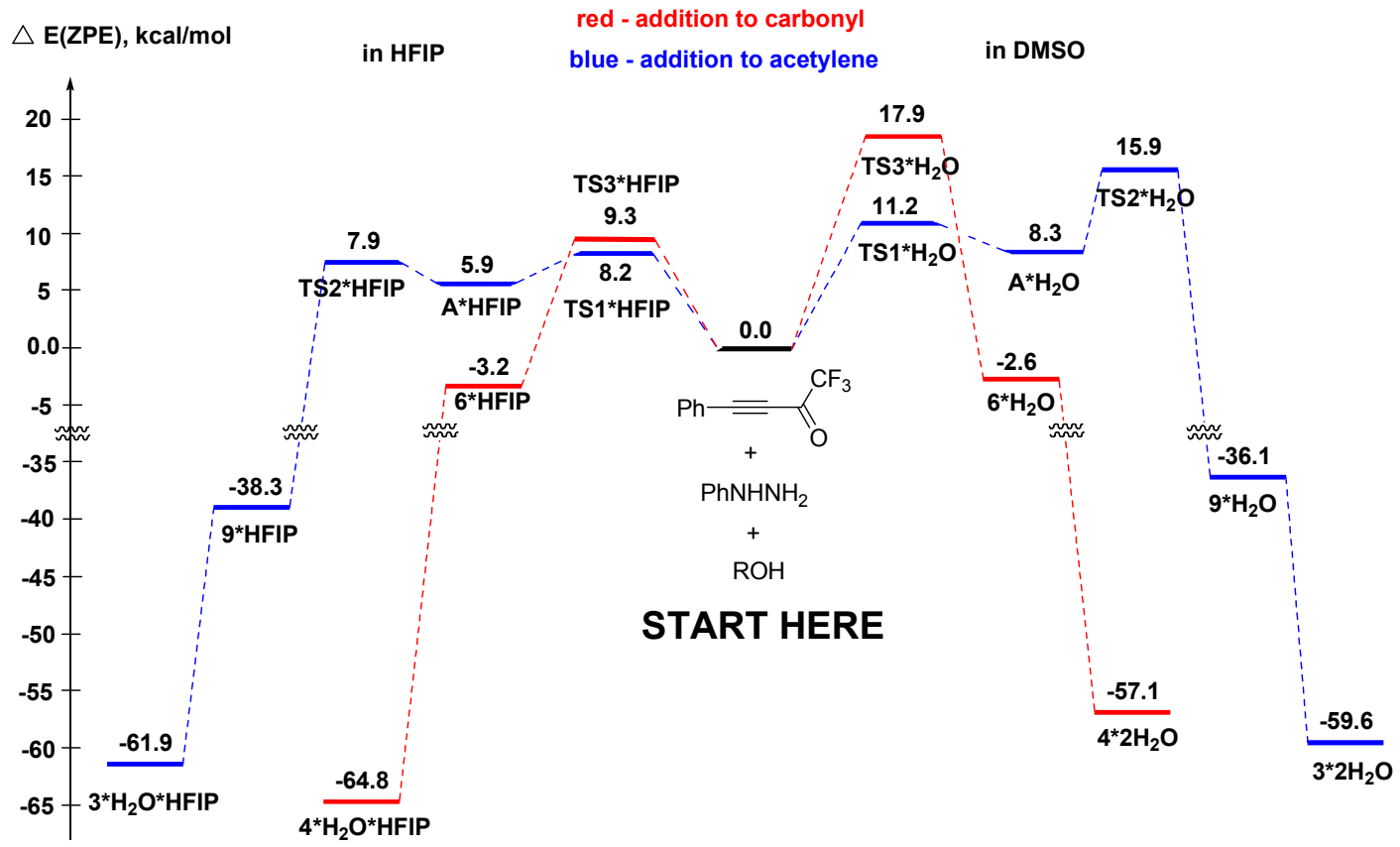


Figure 6. ΔE(ZPE) (kcal/mol) by B3LYP/6-311+G(d,p) for the reaction in HFIP.

Conclusions

It was found that the reaction of trifluoromethylated ynones 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 Celebrex and SC-560 as well as the corresponding regioisomeric molecules.

Experimental Section

NMR spectra were recorded at 600.2 and 400.1 (^{1}H,), 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 DMSO-d_6. Chemical shifts (δ) in ppm are reported with the use of the residual chloroform (7.25 for ^{1}H and 77.0 for ^{13}C), dimethyl sulfoxide (2.49 for ^{1}H 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, CF_3CO_2Et 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 2M HCl at 0-20 °C. Organic layer was separated and water phase was extracted with CH_2Cl_2 (3x30 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 (b.p. = 76-79 °C / 10 Torr). Colorless oil (17.42 g, 88% yield). ^{1}H 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, m.p. 40-42 °C (14.61 g, 62% yield). ^{1}H NMR (400.0 MHz, $CDCl_3$) δ 7.43 (d, J_{HH} = 8.5 Hz, 2H), 7.61 (d, J_{HH} = 8.5 Hz, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 84.0, 98.9, 114.8 (q, J_{CF} = 288.2 Hz, CF_3), 116.5, 129.5, 135.1, 139.3, 167.0 (q, J_{CF} = 42.4 Hz, C=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 (b.p. = 113-116 °C / 10 Torr). Colorless crystals, m.p. 44-46 °C (15.43 g, 56% yield). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 7.53 (d, J_{HH} = 8.4 Hz, 2H, Ar), 7.60 (d, J_{HH} = 8.4 Hz, 2H, Ar). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 84.0, 98.9, 114.8 (q, J_{CF} = 288.6 Hz, CF_3), 116.9, 127.8, 132.4, 135.1, 167.1 (q, J_{CF} = 42.4 Hz, C=O). ^{19}F NMR (376.3 MHz, $CDCl_3$): δ -77.8. IR (ν, cm^{-1}): 1699 (C=O), 2197 (C≡C). HRMS (ESI-TOF): m/z $[M+OH]^-$ Calcd for $C_{10}H_5BrF_3O_2^-$: 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). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 2.43 (s, 3H, CH_3), 7.26 (d, J_{HH} = 8.4 Hz, 2H, Ar), 7.57 (d, J_{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_{CF} = 288.6 Hz, CF_3), 115.0, 129.7, 134.0, 143.8, 167.1 (q, J_{CF} = 42.0 Hz, C=O). ^{19}F NMR (376.3 MHz, $CDCl_3$): δ -78.7. IR (ν, cm^{-1}): 1698 (C=O), 2195 (C≡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, m.p. 48-50 °C (15.20 g, 60% yield). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 1.33 (s, 9H, *t*-Bu), 7.46 (d, J_{HH} = 8.3 Hz, 2H, Ar), 7.61 (d, J_{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_{CF} = 288.0 Hz, CF_3), 115.0, 126.1, 134.0, 156.7, 167.2 (q, J_{CF} = 41.0 Hz, C=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). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 3.86 (s, 3H, OCH_3), 6.93 (d, J_{HH} = 8.9 Hz, 2H, Ar), 7.62 (d, J_{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_{CF} = 288.2 Hz, CF_3), 136.3, 163.2, 167.0 (q, J_{CF} = 41.7 Hz, C=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, m.p. 31-33 °C (9.81 g, 40% yield). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 2.52 (s, 3H, SCH_3), 7.24 (d, J_{HH} = 8.4 Hz, 2H, Ar), 7.56 (d, J_{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_{CF} = 288.6 Hz, CF_3), 125.1, 134.0, 146.4, 166.8 (q, J_{CF} = 42.0 Hz, C=O). ^{19}F NMR (376.3 MHz, $CDCl_3$) δ -78.6. IR (ν, cm^{-1}): 1689 (C=O), 2180 (C≡C). HRMS (ESI-TOF): m/z $[M+OH]^-$ Calcd for $C_{11}H_8F_3O_2S^-$ 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, m.p. 73-75 °C (18.57 g, 67% yield). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 4.00 (s, 3H, OCH_3), 6.69 (d, $^3J_{HH}$ = 8.2 Hz, 1H, Ar), 7.51 (dt, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 0.8 Hz, 1H, Ar), 7.61 (dt, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 0.8 Hz, 1H, Ar), 7.78 (d, $^3J_{HH}$ = 8.2 Hz, 1H, Ar), 8.11 (d, $^3J_{HH}$ = 8.0 Hz, 1H, Ar), 8.24 (d, $^3J_{HH}$ = 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_{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_{CF} = 41.6 Hz, C=O). ^{19}F NMR (376.3 MHz, $CDCl_3$): δ -78.0. IR (ν, cm^{-1}): 1678 (C=O), 2175 (C≡C). HRMS (ESI-TOF): m/z $[M+H]^+$ Calcd for $C_{15}H_{10}F_3O_2^+$ 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, m.p. 83-85 °C (15.38 g, 60% yield). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 4.24-4.31 (m, 4H, OCH_2CH_2O), 6.87 (d, J_{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_{CF} = 288.6 Hz, CF_3), 118.2, 123.0, 128.4, 143.7, 148.2, 166.9 (q, J_{CF} = 41.6 Hz, C=O). ^{19}F NMR (376.3 MHz, $CDCl_3$): δ -78.7. IR (ν, cm^{-1}): 1687 (C=O), 2186 (C≡C). HRMS (ESI-TOF): m/z $[M+Na]^+$ Calcd for $C_{12}H_7F_3O_3Na^+$: 279.0239; found: 279.0235.

1,1,1-Trifluorodec-3-yn-2-one (1j). Purified by vacuum distillation (b.p. = 71-73 °C / 12 Torr). Colorless oil (16.29 g, 79% yield). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 0.89 (t, J_{HH} = 6.7 Hz, 3H), 1.25-1.34 (m, 4H), 1.42

(pent, J_{HH} = 7.3 Hz, 2H), 1.63 (pent, J_{HH} = 7.3 Hz, 2H), 2.49 (t, J_{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 hours. Reaction progress was monitored by ^{19}F NMR. Probes for ^{19}F NMR were prepared by diluting of 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-1*H*-pyrazole (3a). Pale brown powder, m.p. 55-57 °C (Lit. data:[19] 53-54 °C). ^{1}H 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-1*H*-pyrazole (4a). Light yellow powder, m.p. 85-87 °C (Lit. data:[20] 86-88 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 (s, 1H, C^{4}H); 7.15-7.40 (m, 10H, Ph). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 105.7 (q, J = 2 Hz, C^4), 121.5 (q, J = 269 Hz, CF_3), 125.7, 128.6, 128.8, 129.0, 129.1, 129.3, 129.4, 139.4 (2 Ph), 143.4 (q, J = 38 Hz, C^3), 144.9 (C^5). ^{19}F NMR (376.5 MHz, $CDCl_3$): 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-1*H*-pyrazol-5-ol (5a). This compound was not isolated and NMR data were obtained from reaction mixture in DMSO. ^{1}H 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). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 44.0, 93.1 (q, J_{CF} = 31.7 Hz, *C*-CF_3), 118.8, 121.1 (q, J_{CF} = 290.8 Hz, CF_3),

122.0, 125.6, 128.3, 128.7, 129.1, 131.4, 142.5, 146.7. ^{19}F 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 Et_3N. ^{1}H NMR (400.1 MHz, $CDCl_3$): 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). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 81.0 (q, J_{CF} = 31.3 Hz, *C*-CF_3), 82.7, 85.1, 112.2, 117.7, 120.4, 121.8 (q, J_{CF} = 287.5 Hz, CF_3), 127.1, 127.7, 127.8, 130.6, 149.0. ^{19}F NMR (376.3 MHz, $CDCl_3$): δ -82.6.

(*E*)-2-(1,1,1-trifluoro-4-phenylbut-3-yn-2-ylidene)-1-phenylhydrazine (7a). Pale yellow-green needles, m.p. 99-101 °C (Lit. data:[19] 97-99 °C). ^{1}H 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). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 75.6, 104.2, 112.1 (q, J_{CF} = 38.0 Hz, *C*-CF_3), 114.6, 120.5, 121.1 (q, J_{CF} = 270.9 Hz, CF_3), 122.5, 128.8, 129.2, 130.2, 132.0, 142.8. ^{19}F NMR (376.3 MHz, DMSO-d_6): δ -64.9. HRMS (ESI-TOF): m/z $[M+H]^+$ Calcd for $C_{16}H_{12}F_3N_2^+$: 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 hours. After that reaction mixture was poured into ~0.1 M solution of HCl (50 mL), extracted with CH_2Cl_2 (3x20 mL). The combined organic phase was washed with water (50 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel using appropriate mixtures of hexane and CH_2Cl_2 (2:1-1:1, **3a-3m**, **3p**, **3s**, **3t**, **3v**, **3x, 3y**), CH_2Cl_2 (**3n**, **3q**), or mixture of CH_2Cl_2 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-1*H*-pyrazole (3a). Pale brown powder (244 mg, 85% yield). The characterization data (m.p. and NMR) are given in previous section.

3-(4-Chlorophenyl)-5-(trifluoromethyl)-1-phenyl-1*H*-pyrazole (3b). Pale yellow crystals, m.p. 62-64 °C (278 mg, 86% yield). ^{1}H NMR (600.2 MHz, $CDCl_3$): δ 7.10 (s, 1H, CH_{pyr}), 7.44 (d, J_{HH} = 8.4 Hz, 2H, 4-ClC_6H_4), 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-ClC_6H_4). ^{13}C NMR (150.9 MHz, $CDCl_3$): δ 105.9 (q, J_{CF} = 2.2 Hz, CH_{pyr}), 119.6 (q, J_{CF} = 268.5 Hz, CF_3), 125.5, 127.0, 128.9, 129.0, 129.3, 130.2, 133.9 (q, J_{CF} = 39.6 Hz, *C*-CF_3), 134.4, 139.0, 150.4. ^{19}F NMR (564.7 MHz, $CDCl_3$) δ -58.7. The NMR data are in agreement with previously reported.[3]

3-(4-Bromophenyl)-5-(trifluoromethyl)-1-phenyl-1*H*-pyrazole (3c). Light yellow needles, m.p. 62-64 °C (305 mg, 83% yield). ^{1}H NMR (400.1 MHz, $CDCl_3$): 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). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 105.9 (q, J_{CF} = 2.2 Hz, CH_{pyr}), 119.6 (q, J_{CF} = 269.1 Hz, CF_3), 122.7, 125.6, 127.3, 129.1, 129.3, 130.7, 131.9, 133.0 (q, J_{CF} = 39.4 Hz, *C*-CF_3), 139.0, 150.5. ^{19}F NMR (282.4 MHz, $CDCl_3$): δ -58.8. HRMS (ESI-TOF): m/z $[M+H]^+$ Calcd for $C_{16}H_{11}BrF_3N_2^+$: 367.0052; found: 367.0059.

5-(Trifluoromethyl)-1-phenyl-3-*p*-tolyl-1*H*-pyrazole (3d). Pale yellow crystals, m.p. 61-64 °C (266 mg, 88% yield). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 2.43 (s, 3H, Me), 7.13 (s, 1H, CH_{pyr}), 7.29 (d, J_{HH} = 8.0 Hz, 2H, 4-MeC_6H_4), 7.48-7.55 (m, 3H, Ph), 7.60-7.64 (m, 2H, Ph), 7.83 (d, J_{HH} = 8.0 Hz, 2H, 4-MeC_6H_4). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 21.1, 105.8 (q, J_{CF} = 1.8 Hz, CH_{pyr}), 119.8 (q, J_{CF} = 269.4 Hz, CF_3), 125.6, 125.7, 128.9, 129.0, 129.1, 129.4, 133.7, (q, J_{CF} = 39.1 Hz, *C*-CF_3), 138.5, 139.2, 151.7. ^{19}F NMR (282.4 MHz, $CDCl_3$): δ -58.5. The NMR data are in agreement with previously reported.[19]

3-(4-*tert*-Butylphenyl)-5-(trifluoromethyl)-1-phenyl-1*H*-pyrazole (3e). Pale yellow oil (317 mg, 92% yield). ^{1}H NMR (600.2 MHz, $CDCl_3$): 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*-BuC_6H_4), 7.65 (d, J_{HH} = 7.3 Hz, 2H, Ph), 7.91 (d, J_{HH} = 8.4 Hz, 2H, 4-*t*-BuC_6H_4). ^{13}C NMR (150.9 MHz, $CDCl_3$): δ 31.2, 34.6, 105.9 (q, J_{CF} = 2.2 Hz, CH_{pyr}), 119.8 (q, J_{CF} = 268.5 Hz, CF_3), 125.5, 125.6, 125.7, 128.9, 129.0, 129.1, 133.6 (q, J_{CF} = 38.5 Hz, *C*-CF_3), 139.2, 151.6, 151.7. ^{19}F NMR (564.7 MHz, $CDCl_3$): δ -58.5. ^{15}N NMR (40.6 MHz, $CDCl_3$): δ -169.5, -68.6. HRMS (ESI-TOF): m/z $[M+H]^+$ Calcd for $C_{20}H_{20}F_3N_2^+$: 345.1573; found: 345.1573.

5-(Trifluoromethyl)-3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazole (3f). Pale brown crystals, m.p. 76-78 °C (Lit. data:[19] m.p. 77-78 °C) (293 mg, 92% yield). ^{1}H NMR (600.2 MHz, $CDCl_3$): δ 3.86 (s, 3H, MeO), 7.03 (d, J_{HH} = 8.8 Hz, 2H, 4-$MeOC_6H_4$), 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-$MeOC_6H_4$). ^{13}C NMR (150.9 MHz, $CDCl_3$): δ 55.0, 105.5 (q, J_{CF} = 2.2 Hz, CH_{pyr}), 114.1, 119.7 (q, J_{CF} = 268.5 Hz, CF_3), 124.4, 125.6, 127.0, 129.0, 129.1, 133.6 (q, J_{CF} = 38.5 Hz, *C*-CF_3), 139.2, 151.4, 160.0. ^{19}F NMR (564.7 MHz, $CDCl_3$): δ -58.5. The NMR data are in agreement with previously reported.[19]

5-(Trifluoromethyl)-3-(4-(methylthio)phenyl)-1-phenyl-1*H*-pyrazole (3g). Pale brown crystals, m.p. 83-84 °C (287 mg, 86% yield). ^{1}H NMR (600.2 MHz, $CDCl_3$): δ 2.50 (s, 3H, MeS), 7.10 (s, 1H, CH_{pyr}), 7.33 (d, J_{HH} = 8.4 Hz, 2H, 4-$MeSC_6H_4$), 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-$MeSC_6H_4$). ^{13}C NMR (150.9 MHz, $CDCl_3$): δ 15.3, 105.7 (q, J_{CF} = 2.2 Hz, CH_{pyr}), 119.6 (q, J_{CF} = 269.6 Hz, CF_3), 125.5, 126.0, 126.3, 128.3, 128.9, 129.1, 133.6 (q, J_{CF} = 39.6 Hz, *C*-CF_3), 139.1, 139.2, 151.0. ^{19}F NMR (564.7 MHz, $CDCl_3$): δ -58.6. HRMS (ESI-TOF): m/z $[M+H]^+$ Calcd for $C_{17}H_{13}F_3N_2S^+$: 335.0824; found: 335.0825.

5-(Trifluoromethyl)-3-(1-methoxynaphthalen-4-yl)-1-phenyl-1*H*-pyrazole (3h). Pale yellow oil (313 mg, 85% yield). ^{1}H NMR (600.2 MHz, $CDCl_3$): 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). ^{13}C NMR (150.9 MHz, $CDCl_3$): δ 55.3, 103.3, 109.5 (q, J_{CF} = 2.2 Hz, CH_{pyr}), 119.9 (q, J_{CF} = 268.5 Hz, CF_3), 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*-CF_3), 139.2, 151.7, 156.0. ^{19}F NMR (564.7 MHz, $CDCl_3$): δ -58.2. HRMS (ESI-TOF): m/z $[M+H]^+$ Calcd for $C_{21}H_{15}F_3N_2O^+$: 369.1209; found: 369.1209.

5-(Trifluoromethyl)-3-(2,3-dihydrobenzo[b][1,4]dioxin-7-yl)-1-phenyl-1*H*-pyrazole (3i). Pale yellow oil (305 mg, 88% yield). ^{1}H NMR (600.2 MHz, $CDCl_3$): δ 4.25 (s, 4H, -OCH_2CH_2O-), 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). ^{13}C NMR (150.9 MHz, $CDCl_3$): 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, CF_3), 125.2, 125.5, 129.0, 129.1, 133.6 (q, J_{CF} = 38.5 Hz, *C*-CF_3), 139.1, 143.7, 144.1, 151.2. ^{19}F NMR (564.7 MHz, $CDCl_3$): δ -58.6; HRMS (ESI-TOF): m/z [M+H$^+$] Calcd for $C_{18}H_{13}F_3N_2O_2^+$: 347.1002; found: 347.0996.

5-(Trifluoromethyl)-3-hexyl-1-phenyl-1*H*-pyrazole (3j). Pale yellow oil (252 mg, 85% yield). ^{1}H NMR (600.2 MHz, $CDCl_3$): 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 [M+H]$^+$ Calcd for $C_{16}H_{19}F_3N_2^+$: 297.1573; found: 297.1574. The NMR data are in agreement with previously reported.[21]

1-(4-Bromophenyl)-5-(trifluoromethyl)-3-phenyl-1*H*-pyrazole (3k). Pale yellow needles, m.p. 62-64 °C (316 mg, 86% yield). ^{1}H 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 [M+H]$^+$ Calcd for $C_{16}H_{10}BrF_3N_2^+$: 367.0052; found: 367.0050.

5-(Trifluoromethyl)-3-phenyl-1-*p*-tolyl-1*H*-pyrazole (3l). Pale yellow crystals, m.p. 64-66 °C (269 mg, 89% yield). ^{1}H 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 [M+H]$^+$ Calcd for $C_{17}H_{13}F_3N_2^+$: 303.1104; found: 303.1108.

5-(Trifluoromethyl)-1-(3-(trifluoromethyl)phenyl)-3-phenyl-1*H*-pyrazole (3m). Pale yellow oil (338 mg, 95% yield). ^{1}H 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_{3Pyr}), 123.7 (q, J_{CF} = 272.4 Hz, CF_{3Ar}), 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, CF_{3Pyr}), -63.8 (3F, CF_{3Ar}). HRMS (ESI-TOF): m/z $[M+H]^+$ Calcd for $C_{17}H_{10}F_6N_2^+$: 357.0821; found: 357.0823.

4-(5-(Trifluoromethyl)-3-phenyl-1*H*-pyrazol-1-yl)benzonitrile (3n). White crystals, m.p. 85-86 °C (279 mg, 89% yield). ^{1}H 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 $[M+H]^+$ Calcd for $C_{17}H_{10}F_3N_3^+$: 314.0900; found: 314.0902.

3-(5-(Trifluoromethyl)-3-phenyl-1*H*-pyrazol-1-yl)benzoic acid (3o). Pale brown powder, m.p. 138-140 °C (312 mg, 94% yield). ^{1}H 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 $[M+Na^+]$ Calcd for $C_{17}H_{11}F_3N_2O_2Na^+$: 355.0665; found: 355.0658.

5-(Trifluoromethyl)-1-(2-isopropylphenyl)-3-phenyl-1*H*-pyrazole (3p). Pale yellow oil (277 mg, 84% yield). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 1.25 (br s, 6H, $CH(CH_3)_2$), 2.51-2.62 (m, 1H, $CH(CH_3)_2$), 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 $[M+H]^+$ Calcd for $C_{19}H_{17}F_3N_2^+$: 331.1417; found: 331.1418.

5-(Trifluoromethyl)-1-(2,4-dinitrophenyl)-3-phenyl-1*H*-pyrazole (3q). Yellow oil (268 mg, 71% yield). ^{1}H 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)-1*H*-pyrazol-1-yl]benzenesulfonamide (3r). White powder, m.p. 201-203 °C (Lit. data:[23] m.p. 199-201 °C) (312 mg, 85% yield). ^{1}H NMR (400.1 MHz, 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, 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, DMSO-d_6): δ -56.7. The NMR data are in agreement with previously reported.[23]

5-(Trifluoromethyl)-1-(perfluorophenyl)-3-phenyl-1*H*-pyrazole (3s). Colorless crystals, m.p. 85-87 °C (344 mg, 91% yield). ^{1}H 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 (dtt, J_{CF} = 252.8 Hz, J_{CF} = 13.3 Hz, J_{CF} = 2.4 Hz, C_6F_6), 143.0 (dt, J_{CF} = 259.9 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...-145.4 (m, 2F, C_6F_6), -150.0...-150.1 (m, 1F, C_6F_6), -161.4...-161.2 (m, 2F, C_6F_6). HRMS (ESI-TOF): m/z [M+H$^+$] Calcd for $C_{16}H_7F_8N_2^+$: 379.0476; found: 379.0476.

1-(2,6-Dichlorophenyl)-5-(trifluoromethyl)-3-phenyl-1*H*-pyrazole (3t). Pale yellow crystals, m.p. 94-96 °C (343 mg, 96% yield). ^{1}H 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 $[M+H]^+$ Calcd for $C_{16}H_9Cl_2F_3N_2^+$: 357.0168; found: 357.0163.

1-*tert*-Butyl-5-(trifluoromethyl)-3-phenyl-1H-pyrazole (3v). Colorless oil (157 mg, 59% yield). ^{1}H 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)-1*H*-pyrazol-1-yl]benzenesulfonamide (3w). Pale yellow powder, m.p. 180-181 °C (350 mg, 92% yield). ^{1}H 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)-1*H*-pyrazole (3x). Pale yellow crystals, m.p. 79-81 °C (282 mg, 80% yield). ^{1}H 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 $[M+H]^+$ Calcd for $C_{17}H_{12}ClF_3N_2O^+$: 353.0663; found: 353.0665.

3-(4-Chlorophenyl)-5-(trifluoromethyl)-1-(4-methoxyphenyl)-1*H*-pyrazole (3y). Pale yellow-orange crystals, m.p. 105-107 °C (212 mg, 60% yield). ^{1}H 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-ClC_6H_4), 7.44 (d, J_{HH} = 8.9 Hz, 2H, 4-$MeOC_6H_4$), 7.78 (d, J_{HH} = 9.0 Hz, 2H, 4-ClC_6H_4). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 55.5, 105.5 (q, J_{CF} = 1.8 Hz, CH_{pyr}), 114.2, 119.6 (q, J_{CF} = 269.1 Hz, CF_3), 127.0, 127.2, 129.0, 130.3, 131.9, 134.2 (q,

J_{CF} = 39.1 Hz, *C*-CF_3), 134.4, 150.2, 160.2. ^{19}F NMR (376.3 MHz, $CDCl_3$): δ -59.1. HRMS (ESI-TOF): m/z $[M+H]^+$ Calcd for $C_{17}H_{12}ClF_3N_2O^+$: 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 CH_2Cl_2 (2:1-1:1, **4a-m, p-u, s-w, SC-500**), CH_2Cl_2 (**4n**), or mixture of CH_2Cl_2 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 CH_2Cl_2 (3x20 mL). The combined organic phase was washed with water (50 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel using appropriate mixtures of hexane and CH_2Cl_2 (2:1-1:1, **4a,b,f,g,j,k,m,s,x,y,z and 4aa**), CH_2Cl_2 (**4n**), or mixture of CH_2Cl_2 and MeOH (30:1, **4o**, **4r, Celebrex**).

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

5-(4-Chlorophenyl)-3-(trifluoromethyl)-1-phenyl-1*H*-pyrazole (4b). Pale yellow oil (319 mg, 99% yield (**I**); 233 mg, 72% yield (**II**)). ^{1}H NMR (600.2 MHz, $CDCl_3$): δ 6.75 (s, 1H, CH_{pyr}), 7.15 (d, J_{HH} = 8.4 Hz, 2H, 4-ClC_6H_4), 7.28-7.31 (m, 4H), 7.35-7.39 (m, 3H). ^{13}C NMR (150.9 MHz, $CDCl_3$): δ 105.6 (q, J_{CF} = 2.2 Hz, CH_{pyr}), 121.2 (q, J_{CF} = 269.6 Hz, CF_3), 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*-CF_3), 143.4. ^{19}F NMR (564.7 MHz, $CDCl_3$): δ -63.2. The NMR data are in agreement with previously reported.[4c]

5-(4-Bromophenyl)-3-(trifluoromethyl)-1-phenyl-1*H*-pyrazole (4c). Pale yellow crystals, m.p. 104-106 °C (363 mg, 99% yield (**I**)). ^{1}H NMR (600.2 MHz, $CDCl_3$): δ 6.75 (s, 1H, CH_{pyr}), 7.09 (d, J_{HH} = 8.4 Hz, 2H, 4-BrC_6H_4), 7.27-7.32 (m, 2H, Ph), 7.35-7.39 (m, 3H, Ph), 7.45 (d, J_{HH} = 8.4 Hz, 2H, 4-BrC_6H_4). ^{13}C NMR (150.9 MHz, $CDCl_3$): δ 105.6 (q, J_{CF} = 2.2 Hz, CH_{pyr}), 121.1 (q, J_{CF} = 268.5 Hz, CF_3), 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*-CF_3), 143.4. ^{19}F NMR (564.6 MHz, $CDCl_3$): δ -63.3. The NMR data are in agreement with previously reported.[24]

3-(Trifluoromethyl)-1-phenyl-5-*p*-tolyl-1*H*-pyrazole (4d). Pale yellow oil (284 mg, 94% yield (**I**)). ^{1}H NMR (600.2 MHz, $CDCl_3$): δ 2.35 (s, 3H, Me), 6.73 (s, 1H, CH_{pyr}), 7.11 (d, J_{HH} = 8.3 Hz, 2H, 4-MeC_6H_4), 7.13 (d, J_{HH} = 8.3 Hz, 2H, 4-MeC_6H_4), 7.31-7.34 (m, 2H, Ph), 7.35-7.38 (m, 3H, Ph). ^{13}C NMR (150.9 MHz, $CDCl_3$): δ 21.2, 105.2 (q, J_{CF} = 2.2 Hz, CH_{pyr}), 121.3 (q, J_{CF} = 268.5 Hz, CF_3), 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*-CF_3), 144.8. ^{19}F NMR (564.6 MHz, $CDCl_3$): δ -63.3. The NMR data are in agreement with previously reported.[4c]

5-(4-*tert*-Butyl-phenyl)-1-phenyl-3-trifluoromethyl-1*H*-pyrazole (4e). Light brown solid, m.p. 107-108 °C (334 mg, 97% yield (**I**)). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (s, 9H, *t*-Bu), 6.74 (s, 1H, C^4H); 7.15-7.40 (m, 9H, Ar). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 31.3 ($(CH_3)_3$), 34.8 (C^6), 105.5 (C^4); 121.5 (q, J = 269 Hz, CF_3); 125.7, 125.8, 125.9, 126.3, 128.5, 129.2, 139.5 (Ar, Ph); 143.2 (q, J = 38 Hz, C^3); 144.9 (C^5), 152.4 (C^7). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -62.4. ^{15}N NMR (40.6 MHz, $CDCl_3$): δ -165.1, -74.4. IR (KBr, cm^{-1}): ν 1132, 1161 (C-F), 1596, 1620 (C=C, C=N). Anal. Calcd for $C_{20}H_{19}F_3N_2$: 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-1*H*-pyrazole (4f). Pale yellow oil (308 mg, 97% yield (**I**); 273 mg, 86% yield (**II**)). ^{1}H NMR (600.2 MHz, $CDCl_3$): δ 3.78 (s, 3H, MeO), 6.70 (s, 1H, CH_{pyr}), 6.83 (d, J_{HH} = 8.4 Hz, 2H, 4-$MeOC_6H_4$), 7.14 (d, J_{HH} = 8.4 Hz, 2H, 4-$MeOC_6H_4$), 7.30-7.33 (m, 2H, Ph), 7.33-7.37 (m, 3H, Ph). ^{13}C NMR (150.9 MHz, $CDCl_3$): 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, CF_3), 125.4, 128.3, 129.0, 130.0, 139.3, 143.0 (q, J_{CF} = 38.5 Hz, *C*-CF_3), 144.5, 160.0. ^{19}F NMR (564.7 MHz, $CDCl_3$): δ -63.2. The NMR data are in agreement with previously reported.[4c]

3-(Trifluoromethyl)-5-(4-(methylthio)phenyl)-1-phenyl-1*H*-pyrazole (4g). Pale yellow crystals, m.p. 77-80 °C (304 mg, 91% yield (**I**); 267mg, 80% yield (**II**)). ^{1}H NMR (600.2 MHz, $CDCl_3$): δ 2.44 (s, 3H, MeS), 6.73 (s, 1H, CH_{pyr}), 7.12 (d, J_{HH} = 8.4 Hz, 2H, 4-$MeSC_6H_4$), 7.13 (d, J_{HH} = 8.4 Hz, 2H, 4-$MeSC_6H_4$), 7.30-7.33 (m, 2H, Ph), 7.34-7.37 (m, 3H, Ph). ^{13}C NMR (150.9 MHz, $CDCl_3$): δ 14.8, 105.2 (q, J_{CF} = 2.2 Hz, CH_{pyr}), 121.2 (q, J_{CF} = 268.5 Hz, CF_3), 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*-CF_3), 144.1. ^{19}F NMR (564.7 MHz, $CDCl_3$): δ -63.2. HRMS (ESI-TOF): m/z $[M+H]^+$ Calcd for $C_{17}H_{14}F_3N_2S^+$: 335.0824; found: 335.0819.

3-(Trifluoromethyl)-5-(1-methoxynaphthalen-4-yl)-1-phenyl-1*H*-pyrazole (4h). White powder, m.p. 91-93 °C (367 mg, 100% yield (**I**)). ^{1}H NMR (400.1 MHz, $CDCl_3$): 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). ^{13}C NMR (100.6 MHz, $CDCl_3$): 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, CF_3), 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*-CF_3), 156.5. ^{19}F NMR (376.3 MHz, $CDCl_3$): δ -63.1. HRMS (ESI-TOF): m/z $[M+H]^+$ Calcd for $C_{21}H_{16}F_3N_2O^+$: 369.1209; found: 369.1205.

3-(Trifluoromethyl)-5-(2,3-dihydrobenzo[b][1,4]dioxin-7-yl)-1-phenyl-1*H*-pyrazole (4i). Pale yellow crystals, m.p. 122-124 °C (342 mg, 99% yield (**I**)). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 4.19-4.25 (m, 4H, -OCH_2CH_2O-), 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). ^{13}C NMR (100.6 MHz, $CDCl_3$): 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, CF_3), 122.0, 122.2, 125.4, 128.4, 129.0, 139.2, 142.9 (q, J_{CF} = 38.3 Hz, *C*-CF_3), 143.5, 144.3. ^{19}F NMR (376.3 MHz, $CDCl_3$): δ -63.3. HRMS (ESI-TOF): m/z $[M+H]^+$ Calcd for $C_{18}H_{14}F_3N_2O_2^+$: 347.1002; found: 347.1002.

5-Hexyl-1-phenyl-3-trifluoromethyl-1*H*-pyrazole (4j). Light yellow oil (278 mg, 94% yield (**I**); 234 mg, 79% yield (**II**)). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.80-0.90 (m, 3H, CH_3), 1.20-1.35 (m, 6H, CH_2), 1.50-1.65 (m, 2H, CH_2), 2.61 (t, J = 7.8 Hz, 2H, CH_2), 6.45 (s, 1H, C^4H), 7.35-7.55 (m, 5H, Ph). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 14.1, 22.6, 26.3, 28.7, 28.9, 31.5 (Hex), 103.6 (q, J = 2 Hz, C^4), 122.8 (q, J = 269 Hz, CF_3),

125.9, 129.0, 129.4, 139.2 (Ph), 142.9 (q, J = 38 Hz, C^3), 146.0 (C^5). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -62.5. IR (KBr, cm^{-1}): ν 1134, 1179 (C-F), 1559, 1599 (C=C, C=N). Anal. Calcd for $C_{16}H_{19}F_3N_2$: 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-1*H*-pyrazole (4k). White powder, m.p. 73-74 °C (301 mg, 82% yield (**I**); 253 mg, 69% yield (**II**)). ^{1}H NMR (400.1 MHz, $CDCl_3$): 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-BrC_6H_4). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 105.9 (q, J_{CF} = 1.2 Hz, CH_{pyr}), 121.1 (q, J_{CF} = 269.4 Hz, CF_3), 122.2, 126.8, 128.8, 128.9, 129.2, 132.2, 138.2, 143.5 (q, J_{CF} = 38.3 Hz, *C*-CF_3), 144.7. ^{19}F NMR (376.3 MHz, $CDCl_3$): δ -63.5. HRMS (ESI-TOF): m/z $[M+H]^+$ Calcd for $C_{16}H_{11}BrF_3N_2^+$: 367.0058; found: 367.0054.

3-(Trifluoromethyl)-5-phenyl-1-*p*-tolyl-1*H*-pyrazole (4l). Pale yellow crystals, m.p. 86-88 °C (278 mg, 92% yield (**I**)). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 2.36 (s, 3H, Me), 6.73 (s, 1H, CH_{pyr}), 7.13-7.23 (m, 6H), 7.29-7.36 (m, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 21.1, 105.3 (q, J_{CF} = 1.6 Hz, CH_{pyr}), 121.3 (q, J_{CF} = 269.1 Hz, CF_3), 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*-CF_3), 144.5. ^{19}F NMR (376.3 MHz, $CDCl_3$): δ -63.3. HRMS (ESI-TOF): m/z $[M+H]^+$ Calcd for $C_{17}H_{14}F_3N_2^+$: 303.1104; found: 303.1103.

3-(Trifluoromethyl)-1-(3-(trifluoromethyl)phenyl)-5-phenyl-1*H*-pyrazole (4m). Pale yellow crystals, m.p. 66-68 °C (295 mg, 83% yield (**I**); 256 mg, 72% yield (**II**)). ^{1}H NMR (400.1 MHz, $CDCl_3$): 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). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 106.2, 121.1 (q, J_{CF} = 269.1 Hz, CF_{3Pyr}), 122.3 (q, J_{CF} = 4.1 Hz), 123.3 (q, J_{CF} = 272.8 Hz, CF_{3Ar}), 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*-CF_3), 139.6, 143.9 (q, J_{CF} = 38.7 Hz, *C*-CF_3), 145.0. ^{19}F NMR (376.3 MHz, $CDCl_3$): δ -63.5 (3F, CF_{3Pyr}), -64.0 (3F, CF_{3Ar}). HRMS (ESI-TOF): m/z $[M+H]^+$ Calcd for $C_{17}H_{10}F_6N_2^+$: 357.0821; found: 357.0815.

4-(3-(Trifluoromethyl)-5-phenyl-1*H*-pyrazol-1-yl)benzonitrile (4n). Pale yellow crystals, m.p. 88-90 °C (216 mg, 69% yield (**I**); 219 mg, 70% yield (**II**)). ^{1}H NMR (400.1 MHz, $CDCl_3$): 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-CNC_6H_4), 7.63 (d, J_{HH} = 8.6 Hz, 2H, 4-CNC_6H_4). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 106.7 (q, J_{CF} = 1.6 Hz, CH_{pyr}), 111.9, 117.8, 120.9 (q, J_{CF} = 269.4 Hz, CF_3), 125.4, 128.5, 128.8, 129.0, 129.6, 133.0, 142.4, 144.2 (q, J_{CF} = 38.7 Hz, *C*-CF_3), 145.0. ^{19}F NMR (376.3 MHz, $CDCl_3$): δ -63.6. The NMR data are in agreement with previously reported.[25]

3-(3-(Trifluoromethyl)-5-phenyl-1*H*-pyrazol-1-yl)benzoic acid (4o). Pale brown crystals, m.p. 159-162 °C (302 mg, 91% yield (**I**); 329 mg, 99% yield (**II**)). ^{1}H NMR (400.1 MHz, $CDCl_3$): 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, CO_2H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 105.8, 121.1 (q, J_{CF} = 268.7 Hz, CF_3), 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*-CF_3), 144.9, 170.3. ^{19}F NMR (376.3 MHz, $CDCl_3$): δ -63.3. IR (cm^{-1}) ν 1700 (C=O). HRMS (ESI-TOF): m/z $[M-H+2Na]^+$ Calcd for $C_{17}H_{10}F_3N_2O_2Na_2^+$: 377.0484; found: 377.0494.

3-(Trifluoromethyl)-1-(2-isopropylphenyl)-5-phenyl-1*H*-pyrazole (4p). Pale yellow oil (297 mg, 90% yield (**I**)). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 0.90 (br s, 3H, $CH(CH_3)_2$), 1.04 (br s, 3H, $CH(CH_3)_2$), 2.53 (sept, 1H, J_{HH} = 6.9 Hz, $CH(CH_3)_2$), 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). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 22.0-24.9 (m, $CH(CH_3)_2$), 28.0 ($CH(CH_3)_2$), 103.8, 121.3 (q, J_{CF} = 268.7 Hz, CF_3), 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*-CF_3), 145.8, 145.9. ^{19}F NMR (376.3 MHz, $CDCl_3$): δ -63.2. HRMS (ESI-TOF): m/z $[M+H]^+$ Calcd for $C_{19}H_{17}F_3N_2^+$: 331.1417; found: 331.1417.

3-(Trifluoromethyl)-1-(2,4-dinitrophenyl)-5-phenyl-1*H*-pyrazole (4q). Pale yellow oil (19 mg, 5% yield (**I**)). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 6.83 (s, 1 H, 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-di$NO_2C_6H_4$), 8.45 (dd, J_{HH}=8.7, J_{HH}=2.4 Hz, 1H, 2,4-$(NO_2)_2C_6H_4$), 8.77 (d, J_{HH}=2.4 Hz, 1H, 2,4-$(NO_2)_2C_6H_4$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 106.3, 120.6 (q, J_{CF} = 269.4 Hz, CF_3), 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*-CF_3), 146.6, 147.2. ^{19}F NMR (376.3 MHz, $CDCl_3$): δ -63.8. HRMS (ESI-TOF): m/z $[M+H]^+$ Calcd for $C_{16}H_{10}F_3N_4O_4^+$: 379.0649; found: 379.0649.

4-[5-Phenyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (4r). White powder, m.p. 160-162 °C (125 mg, 34% yield (**I**); 297 mg, 81% yield (**II**)). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 5.46 (s, 2H, NH_2), 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-(SO_2NH_2)C_6H_4), 7.84 (d, J_{HH} = 8.6 Hz, 2H, 4-(SO_2NH_2)C_6H_4). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 109.4, 117.7, 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, $CDCl_3$): δ -63.6. The NMR data are in agreement with previously reported.[8]

3-(Trifluoromethyl)-1-(perfluorophenyl)-5-phenyl-1*H*-pyrazole (4s). Pale yellow crystals, m.p. 79-81 °C (8 mg, 2% yield (**I**); 249 mg, 66% yield (**II**)). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 6.84 (s, 1H, CH_{pyr}), 7.24-7.28 (m, 2H, Ph), 7.32-7.47 (m, 3H, Ph). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 105.1, 114.7-115.0 (m, C_6F_6), 120.7 (q, J_{CF} = 269.4 Hz, CF_3), 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, C_6F_6), 142.4 (dt, J_{CF} = 246.2 Hz, J_{CF} = 13.3 Hz, C_6F_6), 143.9 (ddt, J_{CF} = 256.9 Hz, J_{CF} = 7.8 Hz, J_{CF} = 3.9 Hz, C_6F_6), 145.8 (q, J_{CF} = 39.1 Hz, *C*-CF_3), 148.4. ^{19}F NMR (376.3 MHz, $CDCl_3$): δ -63.9 (s, 3F, CF_3), -145.2...-145.4 (m, 2F, C_6F_6), -150.7...-150.9 (m, 1F, C_6F_6), -161.0...-161.2 (m, 2F, C_6F_6). HRMS (ESI-TOF): m/z $[M+H]^+$ Calcd for $C_{16}H_6F_8N_2^+$: 379.0476; found: 379.0469.

3-(Trifluoromethyl)-1-(2,4-dimethylphenyl)-5-phenyl-1*H*-pyrazole (4t). Slight yellow solid, m.p. 92-93 °C (284 mg, 90% yield (**I**); 285 mg, 90% yield (**II**)). ^{1}H NMR (400.1 MHz, $CDCl_3$): 1.92 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 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); ^{13}C NMR (100.6 MHz, $CDCl_3$): 17.3 (CH_3), 21.4 (CH_3), 103.8 (q, J_{CF} = 1.5 Hz, C^4), 121.3 (q, J_{CF} = 268.3 Hz, CF_3), 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-CF_3), 145.6. ^{19}F NMR ($CDCl_3$): -63.3. IR (film, cm^{-1}): 1132, 1163 (C-F), 1569, 1608, 1614 (C=C, C=N, Ph). Anal. Calcd for $C_{18}H_{15}F_3N_2$: 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-1*H*-pyrazole (4u). Orange solid, m.p. 77-78 °C (235 mg, 73% yield (**I**)). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 6.77 (s, 1H, C^4H), 7.20-7.50 (m, 9H, Ar). ^{13}C NMR

(100.6 MHz, $CDCl_3$): δ 106.1 (C^4), 121.4 (q, J_{CF} = 269.0 Hz, CF_3), 126.7, 129.0, 129.0, 129.4, 129.4, 134.1, 134.5 (Ar), 137.9 (C^5), 143.7 (q, J_{CF} = 38.3 Hz, C^3), 145.0 (Ar). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -62.6. IR (film, cm^{-1}): ν 1135, 1163 (C-F), 1572, 1596, 1650 (C=C, C=N, Ph). Anal. Calcd for $C_{16}H_{10}ClF_3N_2$: 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-1*H*-pyrazole (4v). Light yellow solid, m.p. 78-79 °C (238 mg, 75% yield (**I**)). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 3.83 (s, 3H, OCH_3), 6.76 (s, 1H, C^4H), 6.80-6.95 (m, 2H, Ar), 7.20-7.40 (m, 7H, Ar). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 55.6 (OCH_3), 105.3 (C^4), 121.6 (q, J_{CF} = 269.0 Hz, CF_3), 114.4, 127.0, 128.8, 128.9, 129.0, 129.4 (Ar), 132.6 (C^5), 143.0 (q, J_{CF} = 38.3 Hz, C^3), 144.8, 159.7 (Ar). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -62.4. IR (film, cm^{-1}): ν 1132, 1162 (C-F), 1569, 1589, 1610 (C=C, C=N, Ph). Anal. Calcd for $C_{17}H_{13}F_3N_2O$: 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-1*H*-pyrazole (4w). Maize yellow oil (228 mg, 95% yield (**I**); 116 mg, 48% yield (**II**)). ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 15.7 (CH_3), 45.4 (CH_2), 104.5 (C^4), 121.7 (q, J_{CF} = 268 Hz, CF_3), 129.1, 129.1, 129.4, 129.7 (Ph), 141.7 (q, J_{CF} = 38 Hz, C^3), 144.7 (C^5). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -62.3. IR (film, cm^{-1}): ν 1128, 1167 (C-F), 1506, 1608 (C=C, C=N). Anal. Calcd for $C_{12}H_{11}F_3N_2$: 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, m.p. 92-94 °C (117 mg, 44% yield (**I**); 132 mg, 49% yield (**II**)). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.46 (s, 9H), 6.38 (s, 1H), 7.32-7.35 (m, 2H, Ph), 7.38-7.46 (m, 3H, Ph);^{13}C NMR (100.6 MHz, $CDCl_3$): δ 30.9 (CH_3), 62.7 ($\underline{C}(CH_3)_3$), 107.3 (C^4), 121.6 (q, J_{CF} = 268.3 Hz, CF_3), 128.0, 129.0, 130.4, 132.7 (Ph), 139.2 (q, J_{CF} = 37.6 Hz, C^3), 144.0 (C^5). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -62.9. The NMR data are in agreement with previously reported.[8]

1-(2,6-Dichlorophenyl)-3-(trifluoromethyl)-5-phenyl-1*H*-pyrazole (4y). Colorless crystals, m.p. 62-64 °C (296 mg, 83% yield (**II**)). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 6.82 (s, 1H, CH_{pyr}), 7.26-7.41 (m, 8H, Ph). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 104.2 (q, J_{CF} = 1.5 Hz, CH_{pyr}), 121.1 (q, J_{CF} = 269.4 Hz, CF_3), 127.8, 128.3, 128.7, 129.4, 131.4, 135.1, 135.2, 144.5 (q, J_{CF} = 38.7 Hz, *C*-CF_3), 147.2. ^{19}F NMR (376.3 MHz, $CDCl_3$): δ -63.5. HRMS (ESI-TOF): m/z $[M+H]^+$ Calcd for $C_{16}H_9Cl_2F_3N_2^+$: 357.0168; found: 357.0161.

***bis*(4-(3-(Trifluoromethyl)-5-phenyl-1*H*-pyrazol-1-yl)phenyl)methane (4z).** Pale yellow powder, m.p. 138-139 °C (395 mg, 67% yield (**II**)). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 4.01 (s, 2H, CH_2), 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). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 40.9, 105.5 (q, J_{CF} = 1.1 Hz, CH_{pyr}), 121.3 (q, J_{CF} = 269.1 Hz, CF_3), 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*-CF_3), 144.6. ^{19}F NMR (376.3 MHz, $CDCl_3$): δ -63.4. HRMS (ESI-TOF): m/z $[M+Na^+]$ Calcd for $C_{33}H_{22}F_6N_4Na^+$: 611.1641; found: 611.1629.

4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (Celebrex). Pale yellow powder, m.p. 160-161 °C (Lit. data:[23] m.p. 160-162 °C) (328 mg, 86% yield (**II**)). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 2.33 (s, 3H, Me), 5.53 (s, 2H, NH_2), 6.72 (s, 1H, CH_{pyr}), 7.08 (d, J_{HH} = 8.2 Hz, 2H, 4-MeC_6H_4), 7.15 (d, J_{HH} = 8.2 Hz, 2H, 4-MeC_6H_4), 7.40 (d, J_{HH} = 8.6 Hz, 2H, 4-$(SO_2NH_2)C_6H_4$), 7.84 (d, J_{HH} = 8.6 Hz, 2H, 4-$(SO_2NH_2)C_6H_4$). ^{1}H 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-MeC_6H_4), 7.18 (d, J_{HH} = 8.4 Hz, 2H, 4-MeC_6H_4), 7.40 (s, 2H, NH_2), 7.46 (d, J_{HH} = 8.8 Hz, 2H, 4-$(SO_2NH_2)C_6H_4$), 7.86 (d, J_{HH} = 8.8 Hz, 2H, 4-$(SO_2NH_2)C_6H_4$). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 20.7, 105.8, 121.0 (q, J_{CF} = 268.7 Hz, CF_3), 125.2, 125.3, 126.6, 128.5, 129.2, 138.9, 140.9, 142.3 (q, J_{CF} = 38.0 Hz, *C*-CF_3), 143.8, 144.9. ^{19}F NMR (376.3 MHz, DMSO-d_6): δ -62.3. ^{19}F NMR (376.3 MHz, $CDCl_3$): δ -63.6. The NMR data are in agreement with previously reported.[8]

1-(4-Chlorophenyl)-3-(trifluoromethyl)-5-(4-methoxyphenyl)-1*H*-pyrazole (4aa). Pale yellow oil (352 mg, 100% yield (**I**); 314 mg, 89% yield (**II**)). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 3.82 (s, 3H, MeO), 6.70 (s, 1H, CH_{pyr}), 6.88 (d, J_{HH} = 8.8 Hz, 2H, 4-$MeOC_6H_4$), 7.15 (d, J_{HH} = 8.8 Hz, 2H, 4-$MeOC_6H_4$), 7.27 (d, J_{HH} = 8.8 Hz, 2H, 4-ClC_6H_4), 7.34 (d, J_{HH} = 8.8 Hz, 2H, 4-ClC_6H_4). ^{13}C NMR (100.6 MHz, $CDCl_3$): 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, CF_3), 126.5, 129.2, 130.1, 134.1, 137.8, 143.3 (q, J_{CF} = 38.3 Hz, *C*-CF_3), 144.6, 160.2. ^{19}F NMR (376.3 MHz, $CDCl_3$): δ -63.4. The NMR data are in agreement with previously reported.[12a]

5-(4-Chlorophenyl)-3-(trifluoromethyl)-1-(4-methoxyphenyl)-1*H*-pyrazole (SC-560). Yellow oil (321 mg, 91% yield (**I**); 280 mg, 79% yield (**II**)). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 3.81 (s, 3H, MeO), 6.72 (s, 1H, CH_{pyr}), 6.87 (d, J_{HH} = 8.8 Hz, 2H, 4-$MeOC_6H_4$), 7.14 (d, J_{HH} = 8.5 Hz, 2H, 4-ClC_6H_4), 7.20 (d, J_{HH} = 8.8 Hz, 2H, 4-$MeOC_6H_4$), 7.29 (d, J_{HH} = 8.5 Hz, 2H, 4-ClC_6H_4). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 55.5, 105.2, 114.3, 121.2 (q, J_{CF} = 269.1 Hz, CF_3), 126.8, 127.6, 128.9, 129.9, 132.0, 135.0, 142.9 (q, J_{CF} = 38.3 Hz, *C*-CF_3), 143.4, 159.6. ^{19}F NMR (376.3 MHz, $CDCl_3$): 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, m.p. 183-185 °C (45 mg, 12% yield). ^{1}H NMR (400.1 MHz, $CDCl_3$): 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-di$NO_2C_6H_3$), 8.43 (dd, J_{HH} = 9.4 Hz, J_{HH} = 2.4 Hz, 1H, 2,4-$(NO_2)_2C_6H_4$), 9.16 (d, J_{HH} = 2.4 Hz, 1H, 2,4-$(NO_2)_2C_6H_4$), 12.11 (br s, 1H, NH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 74.8, 109.4, 117.7, 119.2, 119.3 (q, J_{CF} = 272.8 Hz, CF_3), 123.0, 125.6 (q, J_{CF} = 39.4 Hz, *C*-CF_3), 129.0, 130.3, 131.4, 132.7, 140.5, 143.1. ^{19}F NMR (376.3 MHz, $CDCl_3$): δ -68.4. IR (cm^{-1}): ν 1342, 1470, 1520, 1620, 2215. HRMS (ESI-TOF): m/z $[M-H]^+$ Calcd for $C_{16}H_8F_3N_4O_4^-$: 377.0503; found: 377.0502.

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

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

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Notes

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