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"Reported, but Still Unknown." A Closer Look into 3,4-Bis- and 3,4,5-Tris(trifluoromethyl)pyrazoles

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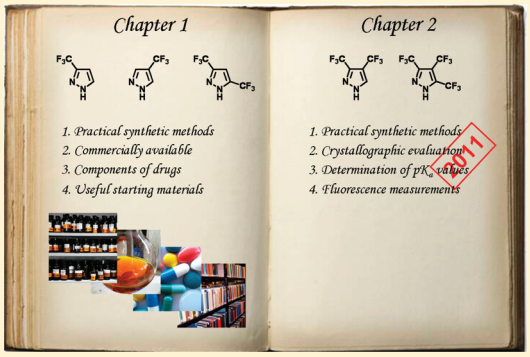
Supporting Information

ABSTRACT: Straightforward practical synthetic approaches to 3,4-bis- and 3,4,5-tris(trifluoromethyl)pyrazoles have been developed. The key step of the both syntheses is a transformation of the carboxylic group in a pyrazole core into the trifluoromethyl group by sulfur tetrafluoride. The elaborated synthetic protocols allow gram-scale preparation of the target products. The obtained compounds are comprehensively characterized by means of crystallographic analysis, determination of pK_a values and fluorescence measurements.



INTRODUCTION

It is now well documented that the incorporation of trifluoromethyl groups into organic molecules can lead to profound changes in their physical, chemical, and especially biological properties.[1,2] Accordingly, an increasing number of trifluoromethyl-substituted derivatives of nitrogen-containing heterocycles have been prepared, which has led to the discovery of novel bioactive products.[3,4] Mono- and bis(trifluoromethyl)-containing pyrazole motifs,[5] in particular, are present in numerous pharmacologically relevant compounds, including those used as inhibitors of the measles virus RNA polymerase complex,[6] inhibitors of CRAC channel,[7] inducers of G0−G1 phase arrest,[8] inhibitors of cyclogenases and 5-lipoxygenase,[9] inhibitors of heat shock protein 90,[10] modulators of AMPA receptor,[11] activators of Kv7/KCNQ potassium channel,[12] regulators of NFAT transcription factor,[13] etc. Others constitute important agrochemicals.[14] Selective COX-2 inhibitors celecoxib[15] and mavacoxib,[16] factor Xa inhibitor razaxaban,[17] and fungicide penthiopyrad[18] are representative examples of the successfully commercialized trifluoromethyl-containing pyrazoles (Figure 1). It is worth noting that trifluoromethylated *NH*-pyrazoles and their derivatives have also found use as bifunctional ligands for transition metals.[19]

Five mono-, bis- and tris-*C*-trifluoromethyl-substituted *NH*-pyrazoles are theoretically possible: 3-trifluoromethylpyrazole (**1**), 4-trifluoromethylpyrazole (**2**), 3,5-bis(trifluoromethyl)-pyrazole (**3**), 3,4-bis(trifluoromethyl)pyrazole (**4**), and 3,4,5-tris(trifluoromethyl)pyrazole (**5**) (Figure 2).

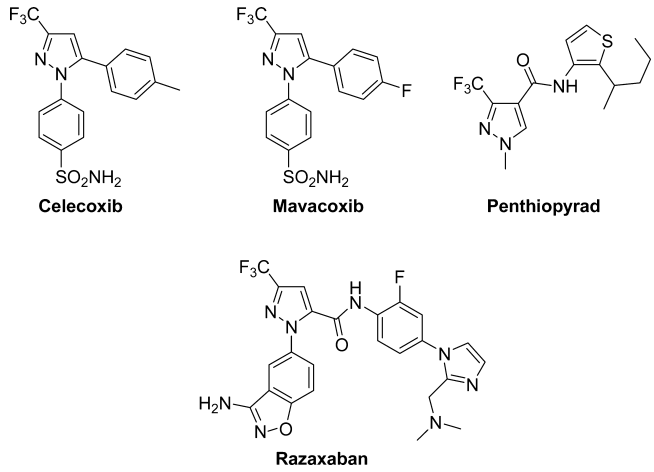


Figure 1. Several marketed trifluoromethyl-containing pyrazole derivatives: celecoxib (antiarthritic), mavacoxib (antiarthritic), penthiopyrad (fungicide), and razaxaban (anticoagulant).

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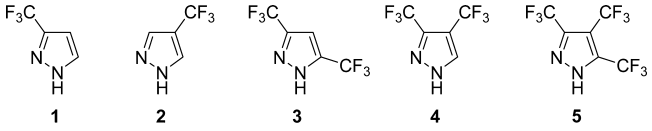


Figure 2. All possible mono- (**1**, **2**), bis- (**3**, **4**), and tris-*C*-trifluoromethyl-substituted (**5**) *NH*-pyrazoles.

Compounds **1**−**3** are commercially available: 91, 7, and 27 companies, respectively, offer them (Table 1, column 2).

Table 1. Comparison of Compounds 1−5[20]

compd	suppliers[a]	reaction[b]/ref[c] (SciFinder)	reaction[b]/ref[c] (Reaxys)	medicinal candidates[d]	agrochemical candidates[e]
1	91	976/74	97/82	363	4912
2	7	0/0	7/5	1	112
3	27	149/39	82/57	27	210
4	0	0/0	0/0	0	2
5	0	0/0	0/0	0	0

[a]According to the "MDL Commercially available materials" database. [b]Number of reactions of the corresponding fluorinated pyrazole. [c]Number of the corresponding literature references. [d]Number of compounds with a motif of the corresponding fluorinated pyrazole in the "MDL Drug data report" database. [e]Number of "agrochemical" compounds with a motif of the corresponding fluorinated pyrazole in the "Symyx Compound index" database.

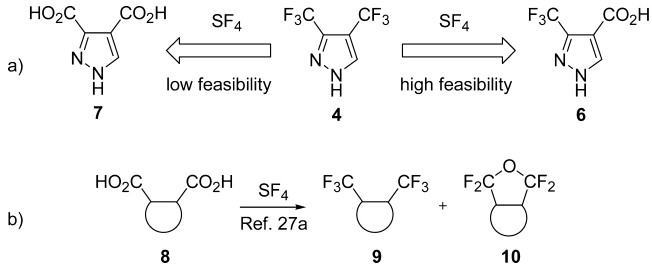
Moreover, according to SciFinder and Reaxys databases, compounds **1**−**3** are often, especially pyrazoles **1** and **3**, used as the starting materials in chemistry, which is reflected in a number of the corresponding publications (Table 1, columns 3 and 4). In addition, motifs of compounds **1**−**3** are frequent within the drug discovery and agrochemical programs (Figure 1; Table 1, columns 5 and 6). In overall, from the data in Table 1, one can easily conclude that among compounds **1**−**5** only pyrazoles **1** and **3** have found a widespread practical application as valuable starting materials and popular bioactive motifs. Much less popularity has been gained by pyrazole **2**. Compounds **4** and **5**, however, despite the great potential, have attracted no attention so far.

Presumably, such a huge difference in the "glory" of trifluoromethylated pyrazoles **1**−**5** is caused by the practicality of the corresponding synthetic approaches to them. Indeed, compounds **1**−**5** are all described in the literature. Pyrazole **1**, in particular, can be prepared by acylation of ethylvinyl ether with trifluoroacetic anhydride followed by cyclization of the obtained intermediate with hydrazine hydrate.[21] Pyrazole **2** is obtained from commercially available 3,3,3-trifluoropropionic acid following a facile two-step procedure.[22] Pyrazole **3**, for example, is easily prepared from hexafluoroacetyl acetone and hydrazine hydrate.[23] Obviously, all of these synthetic procedures are rather routine and can be scaled up to prepare multigram quantities of the target products in high yields, which subsequently results in commercial availability of pyrazoles **1**−**3**. The reported syntheses of pyrazole **4**, in contrast to those of compounds **1**−**3**, commence from the gaseous starting materials diazomethane and bis-(trifluoromethyl)acetylene.[24] Synthesis of pyrazole **5** starts from gaseous trifluoromethyldiazomethane and bis-(trifluoromethyl)acetylene.[25] In addition, no synthesis scale was mentioned for any of pyrazoles **4** and **5**. Taking also into account the low availability of the starting materials, their aggregate state, and explosiveness of diazomethane and trifluoromethyldiazomethane,[26] these synthetic approaches can scarcely be considered as the practical methods to compounds **4** and **5**. As a result, they are not commercially available and consequently have found no practical application in science. In this context, in the present manuscript we describe the gram-scale robust preparation of the both 3,4-bis- (**4**) and 3,4,5-tris(trifluoromethyl)pyrazoles (**5**). The obtained products are comprehensively characterized by means of crystallographic analysis, pK_a determination, and fluorescence measurements. Several application areas for the obtained compounds are also suggested.

RESULTS AND DISCUSSION

Design. Our retrosynthetic approach to pyrazoles **4** and **5** was based on the transformation of the carboxylic group into the trifluoromethyl group by sulfur tetrafluoride (SF_4). Many aliphatic, aromatic, and heteroaromatic carboxylic acids were previously described to react with SF_4 to provide the corresponding trifluoromethylated compounds in good yields.[27] Reaction of a substituted pyrazole carboxylic acid with sulfur tetrafluoride has also been mentioned in a patent.[28] In this context, we came up with an idea of approaching the synthesis of pyrazole **4** by fluorination of monoacid **6** (Scheme 1).

Scheme 1. (a) Retrosynthetic Analysis of Pyrazole 4. (b) General Reaction between the Compounds of Type 8 with Sulfur Tetrafluoride at High Temperatures



Indeed, the reaction of diacid **7** with SF_4 might theoretically also lead to the target compound; however, it was already known from the literature that fluorination of compounds of type **8** usually led to the mixture of the needed bis-trifluoromethylated compound **9** and the side product **10**, which were difficult to separate (Scheme 1).[27a] Therefore, the preference was finally given to monoacid **6** as the starting material.

Accordingly, the synthesis of pyrazole **5** was expected to be performed by fluorination of the carboxylic group in monoacid **11** with SF_4. Recently, Schlosser et al. reported, that lithiation/carboxylation of 1-phenyl-5-(trifluoromethyl)pyrazole afforded the corresponding 1-phenyl-5-(trifluoromethyl)pyrazole-4-carboxylic acid in 62% yield (Scheme 2).[29] Having this in mind, we planned to synthesize acid **11** from the appropriately *N*-protected 3,5-bis(trifluoromethyl)pyrazole **12** analogously to the above-mentioned procedure (Scheme 2).

Chemistry. Synthesis of pyrazole **4** commenced from the commercially available ester **13**. Condensation of compound **13** with triethyl orthoformate in the presence of acetic anhydride smoothly afforded multigram quantities of enone **14** in 79% yield (Scheme 3).[30] Then, the mixture of 1,3-bis-*C*,*C*-electrophile **14** and 1 equiv of hydrazine hydrate in ethanol was stirred at a room temperature for 12 h to form pyrazole **15**

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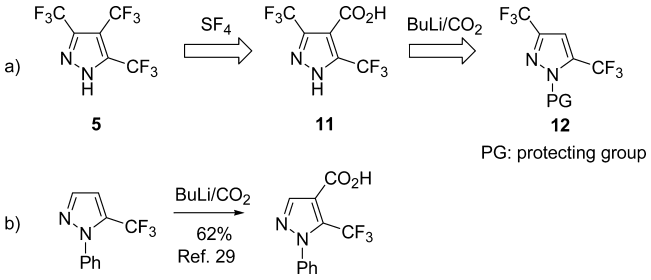
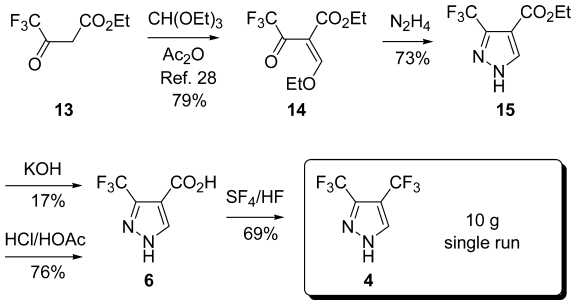
Scheme 2. (a) Retrosynthetic Analysis of Pyrazole 5. (b) Synthesis of 1-Phenyl-5-(trifluoromethyl)pyrazole-4-carboxylic Acid According to Ref 29



Scheme 3. Synthesis of Pyrazole 4



in 73% yield.[31] Hydrolysis of the ester group in compound **15** was attempted next. Under basic reaction conditions (potassium hydroxide in methanol), acid **6** was obtained in only 17% yield, and the formation of unidentified side products was observed.[32] Presumably, the low yield of the target product was caused by a partial hydrolysis of the anionically activated trifluoromethyl group in acid **6**. In fact, similar transformations of 2- and 4-(trifluoromethyl)imidazoles into the corresponding heterocyclic acids by aqueous sodium hydroxide were previously described in the literature.[33] In this context, hydrolysis of the ester group under acidic conditions was also performed. Indeed, heating the suspension of compound **15** in concd HCl/HOAc mixture gave pure acid **6** in 76% yield.

Finally, the key synthesis step, transformation of the carboxylic group into the trifluoromethyl group, was addressed. The reaction of carboxylic acids with sulfur tetrafluoride to provide the trifluoromethylated compounds is a two-step process. The first step readily proceeds already at room temperature to form the corresponding acyl fluoride (Scheme 4, intermediate **A**). The second step is a rate-limiting, and transformation of the initially formed acyl fluoride into the trifluoromethylated compound (Scheme 4, intermediate **B**) usually requires more severe reaction conditions.[27a]

Fluorination of acid **6** was performed under different temperatures to fine tune the product distribution. The reaction progress was monitored by means of ^{19}F NMR. In fact, the reaction of compound **6** with excess of sulfur tetrafluoride in the presence of a catalytic amount of anhydrous HF at room temperature for 12 h resulted in formation of the acyl fluoride only (Table 2, entry 1). Formation of product **4**

Table 2. Reaction of Acid 6 with Sulfur Tetrafluoride under Different Conditions

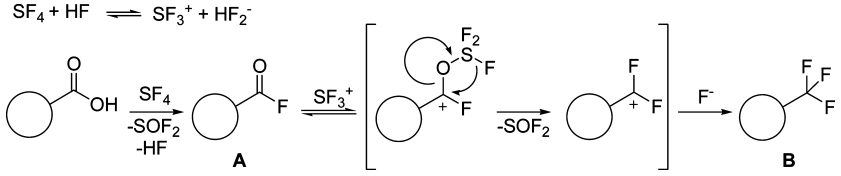
entry	SF_4 quantity (equiv)	reaction time (h)	T (°C)	products[a]
1	3	12	20	**A**
2	3	12	50	**A**/**B** = 70/30
3	3	12	70	**A**/**B** = 20/80
4	3	12	100	**B**

[a]Products ratio was determined by ^{19}F NMR of the crude reaction mixture.

was not observed. Increasing the reaction temperature up to 50 °C gave a mixture, which already contained pyrazole **4**, however, as a minor component (Table 2, entry 2). At 70 °C, the reaction conversion reached 80% (Table 2, entry 3). Finally, performing the reaction at 100 °C gave complete conversion of acid **6** into 3,4-bis(trifluoromethyl)pyrazole (**4**) (Table 2, entry 4). The product was isolated from the reaction mixture by sublimation at a reduced pressure in 69% isolated yield. Importantly, usually acidic protons at heteroatoms, O*H*, N*H*, etc., have to be appropriately protected when performing the reactions with SF_4 in order in ensure the high reaction yield.[34] In our case, however, no *N*-protecting group was required. Consequently, preparation of pyrazole **4** was achieved in four synthetic steps from commercially available compound **13** in 30% overall yield. The developed synthetic protocol was reproducible upon scale up, so that 10 g of the pure material was conveniently prepared in a single batch.

Synthesis of pyrazole **5** started from commercially available diketone **16**. Condensation with hydrazine hydrate in ethanol at room temperature following the literature protocol gave pyrazole **3** in 73% yield (Scheme 5).[23c] Next, a one-pot synthesis of acid **11** from compound **3** was attempted. Lithiation of pyrazole **3** with excess of BuLi followed by addition of dry carbon dioxide, however, was not successful. Only the starting material **3** was isolated from the reaction mixture, thereby indicating that the corresponding bis-anion was not formed. Therefore, as initially planned, we protected a nitrogen atom. The tetrahydropyranyl (THP) moiety was selected as the corresponding *N*-protecting group because (i) it is an electron-donating group, so that it might facilitate the lithiation reaction, (and (ii) both the acid-catalyzed incorporation and cleavage of THP moiety are high yield transformations, which are easily performed even on a large scale.[35] Indeed, heating the mixture of dihydropyran and pyrazole **3** in dichloromethane in the presence of a catalytic amount of *p*-toluenesulfonic acid afforded the *N*-substituted pyrazole **12** in 78% yield after distillation. In fact, compound **12**, in contrast to

Scheme 4. General Two-Step Mechanism for the Reaction of Carboxylic Acids with Sulfur Tetrafluoride To Provide Trifluoromethylated Compounds



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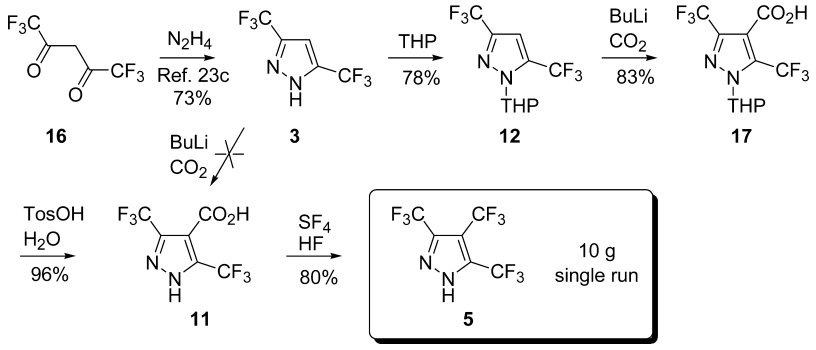
Scheme 5. Synthesis of Pyrazole 5



3, was readily lithiated by BuLi at −80 °C. The subsequent treatment of the formed anion with dry carbon dioxide led to the formation of the protected acid **17** in 83% yield. Unexpectedly, compound **17** rapidly decomposed upon storage, so that once isolated it had to be immediately used in the next synthesis step. Acidic cleavage of the THP-protecting group in **17** smoothly provided *NH*-acid **11** in an excellent yield of 96%. In contrast to compound **17**, acid **11** was stable upon storage. Finally, fluorination of acid **11** by sulfur tetrafluoride according to the protocol previously optimized for the synthesis of pyrazole **4** was performed. Heating compound **11** with excess of SF_4 in the presence of HF in an autoclave at 100 °C afforded a black tarry mixture. Venting off the traces of HF followed by addition of water afforded the crude compound **5** as a solid. Filtration and subsequent crystallization of the product from hexane gave pure pyrazole **5** already as a white solid in 80% isolated yield. The developed synthetic protocol was easily scalable, so that 10 g of the product was conveniently obtained in one synthesis run. The synthesis was performed in five steps from commercially available diketone **16** in 36% overall yield.

An interesting and somewhat surprising experimental result was observed when isolating product **5** from the reaction mixture by extraction with dichloromethane. After drying of the organic phase over sodium sulfate followed by evaporation of the solvent the product was obtained as an oil, which did not crystallize upon prolonged storage. Addition of water, however, initiated the crystallization process. We assumed that the solid product **5** obtained by filtration of the water phase was a hydrate, whereas the oily compound isolated by evaporation of the organic phase did not contain water. Subsequent crystallographic analysis confirmed this suggestion (see the next sections), revealing that pyrazole **5** existed as a semihydrate in the crystal state. A tendency to form the stable hydrate can be attributed to an increased acidity of pyrazole **5** caused by the strong electronegative effect of three trifluoromethyl groups. In fact, the product was insoluble in water; however, it was well soluble in aqueous $NaHCO_3$ solution.

Determination of pK_a Values. Given the fact that pyrazole **5** exhibited the properties of an acid, we reasoned to determine the pK_a values of the both compounds **4** and **5**. Indeed, incorporation of the electron-withdrawing trifluoromethyl group into a pyrazole core increases *NH*-acidity of the parent heterocycle. According to the literature data, for example, the experimental pK_a of unsubstituted pyrazole is 14.2, whereas the pK_a of pyrazole **3** is 7.5, so that the incorporation of two trifluoromethyl groups near the nitrogen atoms leads to $\Delta pK_a = -6.7$ (Figure 3).[36]

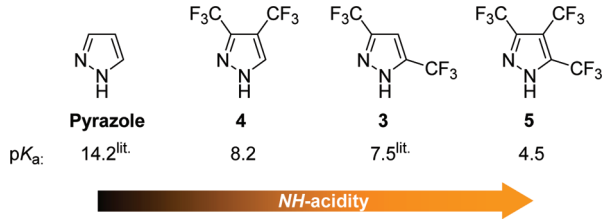


Figure 3. Comparison of *NH*-acidities of pyrazole and compounds **3**–**5**.

The determination of pK_a values of compounds **4** and **5** was made by potentiometric titration with a glass electrode (Supporting Information). The measured the pK_a of pyrazole **4** was 8.2, while the pK_a of pyrazole **5** had an extremely high value of 4.5, indicating thereby the compound to be even more acidic than acetic acid with pK_a = 4.7! It is worth mentioning that the trifluoromethyl group near the nitrogen atom at the C-3 (C-5) position of the pyrazole core, as expected, has a larger influence on pK_a than the corresponding substituent at the fourth position. In fact, pyrazole **3** is significantly stronger acid than pyrazole **4** with $\Delta pK_a = -0.7$. The corresponding decrement of trifluoromethyl group at the C-3 (C-5) position of the pyrazole ring is easily calculated from pK_a values of unsubstituted pyrazole and 3,5-bis(trifluoromethyl)pyrazole (**3**): $\Delta pK_a = (7.5 - 14.2)/2 \approx -3.4$. The impact of the trifluoromethyl group at the C-4 position can be determined from the difference in acidities of 3,5-bis(trifluoromethyl)-pyrazole (**3**) and 3,4,5-tris(trifluoromethyl)pyrazole (**5**): $\Delta pK_a = 4.5 - 7.5 = -3.0$. In this context, the calculated pK_a of pyrazole **4** is expected to be 14.2 − 3.0 − 3.4 = 7.8, which is slightly under the measured value of 8.2. This discrepancy, however, can be explained by existence of the compound in two tautomeric forms, which is not the case for any of the pyrazoles **3**, **5**, and the unsubstituted one.

Fluorescence Measurements. With the aim to characterize the obtained compounds in a comprehensive manner and driven by curiosity, we have also studied the fluorescence properties of pyrazoles **4** and **5**. Unexpectedly, a bright feature was discovered, which we would like to highlight here briefly. Fluorescence emission spectra of the both compounds in dimethyl sulfoxide solution under excitation at 277 nm are characterized by two maxima at 326 and 456 nm (Supporting Information). The maximum of fluorescence intensity (I_{max}) of pyrazole **4** is observed at 326 nm, whereas I_{max} of pyrazole **5** is at 456 nm. This shift clearly reveals for the significant redistribution of electronic properties upon incorporation of the additional trifluoromethyl group into pyrazole **4**.[37]

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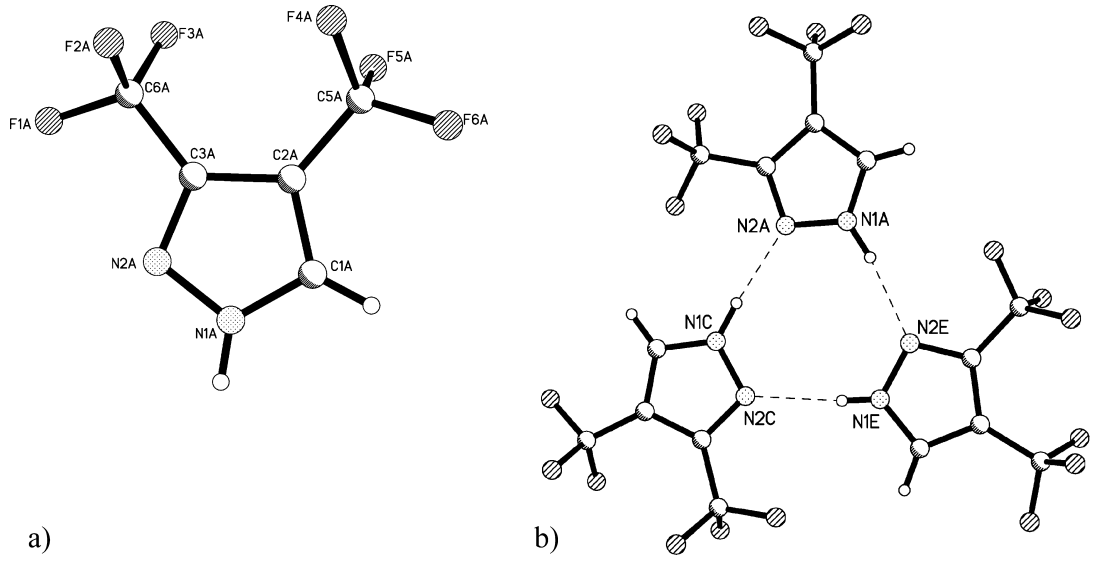

Figure 4. (a) Molecular structure of pyrazole **4**. (b) Trimer of pyrazole **4** formed in the crystal phase.

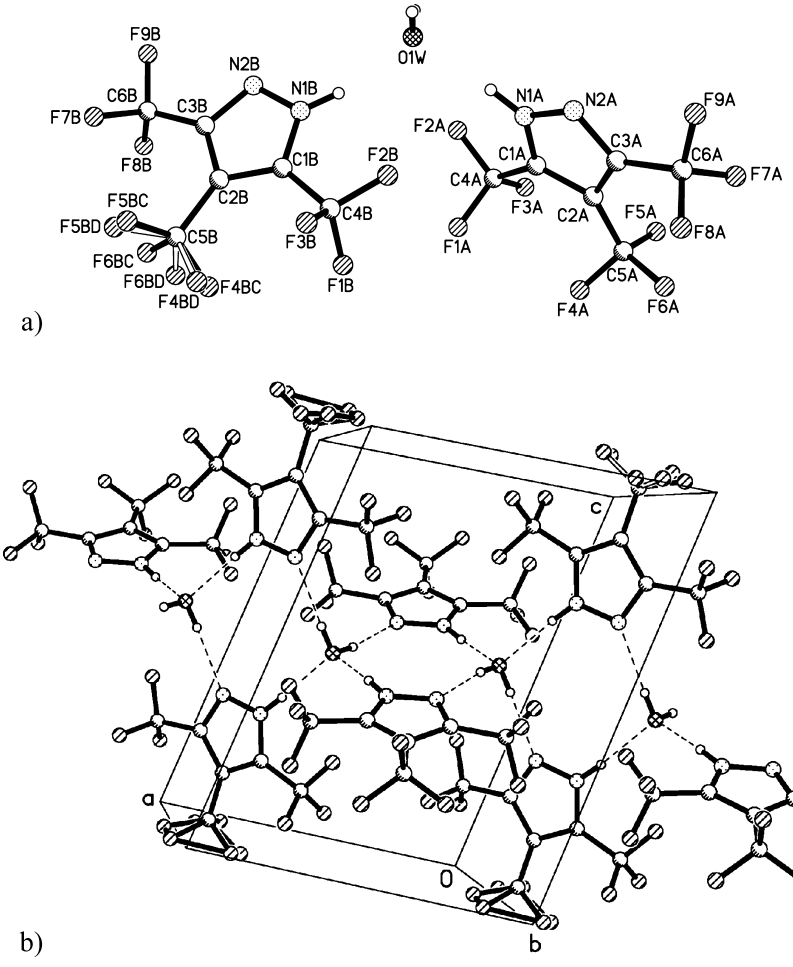

Figure 5. (a) Molecular structure of pyrazole **5**. (b) Packing of pyrazole **5** in the crystal phase.

Crystallographic Analysis. To reveal the impact of trifluoromethyl groups on the pyrazole molecule geometry, crystallographic analysis of the both pyrazoles **4** and **5** was performed (Figures 4 and 5). Crystals of compound **4**, suitable for an X-ray diffraction study, were obtained by a slow evaporation of a diluted solution of **4** in dioxane.

Six molecules (A–F) of pyrazole **4** are observed in the asymmetric part of the unit cell forming two trimers due to the N–H···N hydrogen bonds (Figure 4). The A, E, and C molecules are bonded by the N(2A)–H···N(1E)′ (1 − *x*, − *y*, − *z*) H···N 2.00 Å N–H···N 172°; N(2E)–H···N(1C)′ (0.5 + *x*, −0.5 − *y*, *z* − 0.5) H···N 2.07 Å N–H···N 175°; N(2C)–

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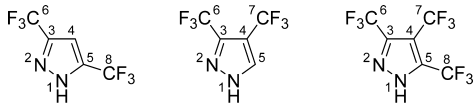
Table 3. Selected Bond Lengths (Å) in Pyrazoles 3− According to X-ray Data[a]



3 4 5

bond	compd 3[b]	compd 4 (molecule A)	compd 5 (molecule A)	compd 5 (molecule A)
N(1)−N(2)	1.348	1.342−1.346	1.344	1.337
N(2)−C(3)	1.351	1.319−1.334	1.335	1.330
C(3)−C(4)	1.391	1.401−1.406	1.387	1.390
C(4)−C(5)	1.387	1.369−1.378	1.387	1.385
C(5)−N(1)	1.348	1.331−1.339	1.324	1.337
C(3)−C(6)	1.483	1.482−1.491	1.494	1.493
C(4)−C(7)		1.472−1.479	1.484	1.484
C(5)−C(8)	1.482		1.496	1.502

[a]For convenience, atom numbering in pyrazole **5** was also used for pyrazoles **3** and **4**. In that numbering, thus, C_7 in pyrazole **3** does not exist. [b]Data are taken from ref 38.

H···N(1A) (0.5 − *x*, y − 0.5, 0.5 − z) H···N 1.98 Å N−H···N 175° hydrogen bonds and the B, D, and F molecules form second trimer due to the intermolecular hydrogen bonds N(2B)−H···N(1D)′ (*x* − 0.5, −0.5 − *y*, *z* − 0.5) H···N 1.96 Å N−H···N 177°; N(2D)−H···N(1F)′ (1.5 − *x*, *y* − 0.5, 0.5 − *z*) H···N 2.01 Å 173°; N(2F)−H···N(1B)′ (1 − *x*, − *y*, − *z*) H···N 1.98 Å N−H···N 172°.

Crystals of compound **5**, suitable for an X-ray diffraction study, were obtained by evaporation of a diluted solution of **5** in hexane. Compound **5** exists as a semihydrate in crystal phase (Figure 5a). Water is supposed to play a crucial role in the formation of the crystal structure: the molecules of compounds **5** form infinite chains along the crystallographic direction [1 0 0] where they are combined over "bridge" molecules of water. The crystalline lattice is formed in such a way that the hydrophobic trifluoromethyl groups are pointed out of the simplest structural lattice unit, whereas hydrophilic nitrogen atoms connected by water molecules are placed in the middle of this unit (Figure 5b). There are two types (ratio 68:32) of pyrazole **5** molecules with different orientation of the trifluoromethyl group at the fourth of the pyrazole ring present in the crystalline state.

Having in hand the crystallographic information on the both pyrazoles **4** and **5**, we compared their bond lengths in crystal state with those reported for pyrazole **3**.[38] It is known that in pyrazole **3** C(3)−C(4) and C(4)−C(5)/C(3)−C(6) and C(5)−C(8) bond lengths are almost equal (1.391 Å and 1.387 Å/1.383 Å and 1.382 Å, correspondingly) (Table 3). The same is true for pyrazole **5**, as C(3)−C(4) and C(4)−C(5)/C(3)−C(6) and C(5)−C(8) are also very close/identical, because of the symmetric structure. It is worth noting that incorporation of the additional trifluoromethyl group at the fourth of pyrazole **3**, compound **5**, does not have any impact on C(3)−C(4) and C(4)−C(5); however, it significantly affects both C(3)−C(6) and C(5)−C(8). For example, in pyrazole **5**, C(3)−C(4) and C(4)−C(5) (1.387 Å, molecule A; 1.390 Å and 1.385 Å, molecule B) are very close to those in pyrazole **3**. However, C(3)−C(6) and C(5)−C(8) bond lengths in pyrazole **5** are elongated by 0.010−0.015 Å compared to those in pyrazole **3**, presumably due to a repulsion between three bulky trifluoromethyl groups.

In pyrazole **4**, in contrast to symmetric compounds **3** and **5**, the bond C(3)−C(4) is significantly longer than C(4)−C(5) (1.401−1.406 Å vs 1.369−1.378 Å) due to a repulsion between two adjacent trifluoromethyl groups. Moreover, the C(3)−C(4) bond in pyrazole **4** is longer than that in compounds **3** and **5** by ∼0.015 Å; however, the corresponding C(4)−C(5) is shorter by ∼0.010 Å. It is also worth noting that C(4)−C(7) in pyrazole **5** is slightly longer than that in pyrazole **4** again as the result of repulsion between trifluoromethyl groups: the CF_3 group at the 4-position of the pyrazole ring in compound **5** has two adjacent trifluoromethyl groups, whereas that in compound **4** has only one.

Application area. Having developed a reliable and scalable procedures to both pyrazoles **4** and **5**, and having characterized their *NH*-acidities, molecular structures, and fluorescent properties, we want also to briefly highlight here several, in our opinion, of the most interesting application areas for these compounds.

1. Pharmaceuticals and Agricultural Products. As already mentioned in the introduction, the trifluoromethylated pyrazole motif frequently occurs in medicinal chemistry and agrochemistry. This is because of at least two reasons. First, the pyrazole core is historically being used as a small structural template in the preparation of novel bioactive compounds.[39] On the other hand, the trifluoromethyl group is another prominent structural unit because of its ability to effectively fine-tune physicochemical and pharmakinetic compound properties.[1−4] Hence, simple combination of two popular structural elements[40] leads to conceptually attractive trifluoromethyl-substituted pyrazole motif.

Functionalization of trifluoromethylated *NH*-pyrazoles at the *N*-terminus can be achieved by alkylation, arylation, and epoxide ring-opening reactions[41] leading to diverse compound libraries. As an example, we mention here the very recent research work published by Merck on the discovery of novel positive modulators of AMPA receptor.[42] The authors reported on the identification of high-throughput screening derived hit **18** bearing trifluoromethylated pyrazole unit. With the aim of improving compound solubility and metabolic stability, a rational drug-design approach was applied to find the lead structure **19** (Scheme 6). The key step in the synthesis of all corresponding compounds within this drug discovery program was *N*-alkylation of various trifluoromethylated *NH*-pyrazoles. Importantly, nonsymmetrical *NH*-pyrazoles bearing a trifluoromethyl group at the position 3(5) of the pyrazole core stereoselectively react at the less sterically hindered *N*-terminus to provide only one isomer among two possible.

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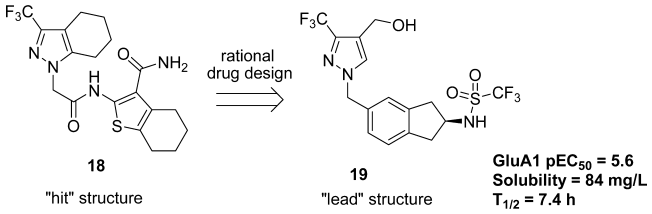
Scheme 6. "Hit-to-Lead" Optimization Program Published by Merck[42,a]



[a]Both "hit" and "lead" structures possess a trifluoromethyl-substituted pyrazole motif.

In this context, with scalable synthesis pyrazole **4** already seems to be a highly promising starting material for medicinal chemistry and drug discovery, in the very same way as its isomer, pyrazole **3**, already is. In addition, both pyrazole **4** with six fluorine atoms and especially pyrazole **5** having nine fluorine atoms are attractive candidates for agrochemistry, the field in which polyfluorinated heterocyclic derivatives are prevailing.[14,43]

2. Transition-Metal Ligands. Diverse pyrazole derivatives, including those containing trifluoromethyl groups, are being used in coordination chemistry on a routine basis.[19,44] To demonstrate the potential of pyrazoles **4** and **5** as the ligands, we refer here to several recent examples randomly taken from a literature on the preparation and subsequent structural characterization of complexes of copper, platinum, gold, and another transition metals with trifluoromethylated pyrazoles **1** and **3**, reported by different research groups.[19] For instance, Dias and co-workers beneficially used the electron-withdrawing property of these compounds to obtain the stable complexes of ethylene and carbon monoxide: compounds **20** and **21**, correspondingly (Figure 6).[19b−d]

Figure 6. Structure of stable transition metal complexes of ethylene and carbon monoxide (**20** and **21**) with pyrazoles **1** and **3**.[19b−d]

Also worth mentioning is the work of Togni et al. where the authors used pyrazole **3** to prepare rhodium complexes with ferrocenyl ligand **22** in order to reveal the role of electronic effects on the enantioselectivity of catalytic hydroboration reaction (Figure 7).[45]

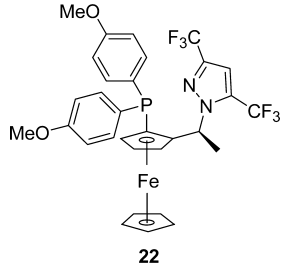


Figure 7. Structure of model ligand **22**.[45]

Taking into account the obvious electron-withdrawing nature of the both compounds **4** and **5**, they indeed seem to be intriguing yet undiscovered ligands for coordination chemistry.

■ CONCLUSION

In summary, we have developed the first reliable and scalable synthetic protocols to 3,4-bis(trifluoromethyl)pyrazole (**4**) and 3,4,5-tris(trifluoromethyl)pyrazole (**5**). The key step of the both syntheses was a transformation of the carboxylic group into the trifluoromethyl group in the corresponding acids **6** and **11** by sulfur tetrafluoride. The developed procedures allowed gram-scale preparation of pyrazoles **4** (10 g) and **5** (10 g) in one synthesis run. The obtained products were comprehensively characterized by means of crystallographic analysis, determination of pK_a values, and fluorescence measurements. With rapid scalable synthesis, we believe the pyrazoles **4** and **5** to find wide application soon in medicinal chemistry and agrochemistry as novel unexplored building blocks and in coordination chemistry as promising ligands for transition metals.

■ EXPERIMENTAL SECTION

Solvents were purified according to standard procedures. All reactions were performed in argon atmosphere. Other starting materials were taken at Enamine. Column chromatography was performed using Kieselgel Merck 60 (230−400 mesh) as the stationary phase. ^{1}H-, ^{19}F-, ^{13}C NMR spectra were recorded on at 499.9 MHz, 470.3 and 124.9 MHz. Chemical shifts are reported in ppm downfield from TMS (^{1}H, ^{13}C) or $CFCl_3$ (^{19}F) as internal standards. Mass spectra were recorded on GC/MS instrument by electronic ionization (EI).

Ethyl 3-Ethoxy-2-(trifluoroacetyl)acrylate (14). A mixture of compound **13** (184 g, 1 mol), $CH(OEt)_3$ (296 g, 2 mol), and Ac_2O (306 g, 3 mol) was heated at reflux for 5 h. The reaction mixture was distilled at a reduced pressure to provide pure compound **14** (190 g, 790 mmol, 79% yield) as a colorless liquid. Bp: 115 °C/0.2 mm. NMR data are identical to those reported previously.[30]

Ethyl 3-(Ttrifluoromethyl)pyrazole-4-carboxylate (15). A solution of compound **14** (70.0 g, 292 mmol) and 70% hydrazine hydrate (20.8 g, 292 mmol) in EtOH (1000 mL) was stirred at a room temperature for 12 h. The solvent was evaporated under vacuum. The residue was purified by flash column chromatography using CH_2Cl_2 as an eluent to provide pure pyrazole **15** (44.2 g, 212 mmol, 73% yield) as a yellow solid. Mp: 136−137 °C. ^{1}H NMR (500 MHz; DMSO-d_6; Me_4Si), δ: 13.92 (1H, broad s, N*H*), 8.55 (1H, s, C*H*), 4.25 (2H, q, ^3J(H,H) = 7.0 Hz, OCH_2CH_3), 1.27 (3H, t, ^3J(H,H) = 7.0 Hz, OCH_2CH_3). ^{13}C NMR (125 MHz; DMSO-d_6; Me_4Si), δ: 161.0 (s), 140.8 (q, ^2J(C,F) = 37.5 Hz), 136.2 (s), 121.4 (q, ^1J(C,F) = 267.5 Hz), 112.0 (s), 60.29 (s), 14.4 (s). ^{19}F NMR (376 MHz; DMSO-d_6; $CFCl_3$), δ: −60.20 (s, CF_3). MS (m/z): 208 (M^+). Anal. Calcd for $C_7H_7F_3N_2O_2$: C, 40.39; H, 3.39; N, 13.46. Found: C, 40.01; H, 3.61; N, 13.07.

3-(Trifluoromethyl)pyrazole-4-carboxylic Acid (6). *Method A.* A solution of pyrazole **15** (10.0 g, 48 mmol) and KOH (5.4 g, 96 mmol) in MeOH (100 mL) was heated at reflux under stirring for 2 h. After the solution was cooled to room temperature, the solvent was evaporated under vacuum. Water (100 mL) was added, and the pH value of the obtained solution was adjusted to 4−5 by adding 12 N aq HCl. The formed solid was filtered off and dried in air. Et_2O (300 mL) was added, and the suspension was heated at reflux for 10 min. The insoluble residue was filtered off and discarded. The filtrate was evaporated under vacuum. The formed solid residue was crystallized from Et_2O−hexane mixture to provide the pure acid **6** (1.5 g, 8.3 mmol, 17% yield) as a yellow solid. Mp: 253−254 °C.

Method B. A suspension of pyrazole **15** (40.0 g, 192 mmol) in 12 N aq HCl (300 mL) and HOAc (60 mL) was heated at reflux under stirring for 6 h. After the suspension was cooled to room temperature, the solvent was evaporated under vacuum. The solid residue was

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crystallized from Et_2O–hexane mixture to obtain the pure acid **6** (26.3 g, 146 mmol, 76% yield) as a yellow solid. Mp: 249–250 °C. ^{1}H NMR (500 MHz; DMSO-d_6; Me_4Si), δ: 13.92 (1H, broad s, N*H*), 12.71 (1H, broad s, O*H*), 8.43 (1H, s, C*H*). ^{13}C NMR (125 MHz; DMSO-d_6; Me_4Si), δ: 162.5 (s), 140.8 (q, ^2J(C,F) = 38.8 Hz), 136.2 (s), 121.5 (q, ^1J(C,F) = 267.5 Hz), 113.0 (s). ^{19}F NMR (376 MHz; DMSO-d_6; $CFCl_3$), δ: −59.98 (s, CF_3). MS (*m*/*z*): 180 (M^+). Anal. Calcd for $C_5H_3F_3N_2O_2$: C, 33.35; H, 1.68; N, 15.56. Found: C, 33.20; H, 1.91; N, 15.21.

3,4-Bis(trifluoromethyl)pyrazole (4). A mixture of acid **6** (18.0 g, 100 mmol), anhydrous HF (2 mL), and SF_4 (32.4 g, 300 mmol) was kept in a stainless steel autoclave at 100 °C for 12 h. The gaseous products were removed under an effective fume hood. The tarry residue was placed into a Teflon dish and was heated at 40 °C for additional 1 h to remove traces of HF. The obtained raw material was purified by double sublimation at 85 °C at 20 mm to give pure pyrazole **4** (14.1 g, 69 mmol, 69% yield) as a white solid. Mp: 124–126 °C (sublimation). Crystals of compound **4**, suitable for an X-ray diffraction study were obtained by a slow evaporation of a diluted solution of **4** in dioxane. ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si), δ: 14.40 (1H, broad s, N*H*), 8.70 (1H, s, C*H*). ^{13}C NMR (125 MHz; DMSO-d_6; Me_4Si), δ: 137.9 (q, ^2J(C,F) = 37.5 Hz), 133.2 (s), 122.3 (q, ^1J(C,F) = 265.0 Hz), 121.0 (q, ^1J(C,F) = 266.3 Hz), 109.7 (q, ^2J(C,F) = 38.8 Hz). ^{19}F NMR (470 MHz; $CDCl_3$; $CFCl_3$), δ: −55.92 (s, CF_3), −51.12 (s, CF_3). MS (*m*/*z*): 204 (M^+). Anal. Calcd for $C_5H_2F_6N_2$: C, 29.43; H, 0.99; N, 13.73. Found: C, 29.05; H, 0.90; N, 13.51.

3,5-Bis(trifluoromethyl)-1*H*-pyrazole (3).[23c] To a solution of diketone **16** (40.8 g, 196 mmol) in ethanol (300 mL) was added hydrazine hydrate (10.5 g, 210 mmol). The reaction mixture was heated at reflux for 15 h. The solvent was removed under vacuum. The residue was distilled at atmosphere pressure to obtain compound **3** (30 g, 147 mmol, 73%) as a white solid. Bp: 146–147 °C. Mp: 84–85 °C (lit:[23c] mp 71–72 °C). NMR data are identical to those reported previously.[23c]

1-(Tetrahydro-2*H*-pyran-2-yl)-3,5-bis(trifluoromethyl)-1*H*-pyrazole (12). A solution of pyrazole **3** (29.0 g, 142 mmol), dihydropyran (11.9 g, 142 mmol) and TsOH (0.3 g) in CH_2Cl_2 (100 mL) was heated at reflux for 5 h. The solvent was evaporated under vacuum. The residue was distilled under reduced pressure to give pure compound **12** as a colorless liquid (32.0 g, 111 mmol, 78% yield). Bp: 56–57 °C/1 mm. ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si), δ: 6.94 (1H, s, C*H*), 5.56 (1H, dd, ^3J = 8.5, 2.5 Hz, OC*H*), 4.05 (1H, m, OC*H*H), 3.71 (1H, m, OCH*H*), 2.48 (1H, m), 2.14 (1H, m), 2.03 (1H, m), 1.74 (2H, m), 1.65 (1H, m). ^{13}C NMR (125 MHz; $CDCl_3$; Me_4Si), δ: 142.1 (q, ^2J(CF) = 39.4 Hz), 133.9 (q, ^2J(CF) = 40.5 Hz), 120.6 (q, ^1J(CF) = 268.7 Hz), 119.3 (q, ^1J(CF) = 270.1 Hz), 106.8 (br s), 86.6 (s), 67.8 (s), 29.2 (s), 24.6 (s), 22.0 (s). ^{19}F NMR (470 MHz; $CDCl_3$; $CFCl_3$), δ: −60.14 (s, 3F, CF_3), −62.97 (s, 3F, CF_3). MS (*m*/*z*): 288 (M^+). Anal. Calcd for $C_{10}H_{10}F_6N_2O$: C, 41.68; H, 3.50; N, 9.72. Found: C, 41.33; H, 3.77; N, 9.49.

1-(Tetrahydro-2*H*-pyran-2-yl)-3,5-bis(trifluoromethyl)-1*H*-pyrazole-4-carboxylic Acid (17). A solution of 1.6 M BuLi in hexane (52 mL, 83 mmol) was added to a solution of compound **12** (24.0 g, 83 mmol) in THF (250 mL) at −80 °C. The mixture was stirred at this temperature for 15 min followed by addition of dry solid CO_2 (20 g, 455 mmol). The reaction mixture was stirred at −80 °C for 1 h and subsequently at a room temperature for 1 h. The solvent was removed under vacuum, the residue was treated with water (100 mL), and the mixture was carefully acidified by 12 N HCl. The formed precipitate was filtered off, washed with water and dried on air to give acid **17** (23.0 g, 69 mmol, 83% yield) as a white solid. Mp: 80–85 °C dec. The obtained material was of ∼90% purity. ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si), δ: 6.30–5.30 (1H, br s, CO_2H), 5.69 (1H, m, OC*H*), 3.98 (1H, m, OC*H*H), 3.73 (1H, m, OC*H*H), 2.50 (1H, m), 2.16 (1H, m), 2.09 (1H, m), 1.80–163 (3H, m). The compound decomposes rapidly upon storage and has to be immediately used in the next step without additional purification.

3,5-Bis(trifluoromethyl)pyrazole-4-carboxylic Acid (11). A solution of compound **17** (16.2 g, 48 mmol) and concd HCl (0.6 mL) in MeOH (60 mL) was heated at reflux for 2 h. The solvent was removed under vacuum. The residue was crystallized from water (100 mL) to obtain pure acid **11** (11.6 g, 46 mmol, 96% yield) as a white solid. Mp > 250 °C (sublimation). ^{1}H NMR (500 MHz; DMSO-d_6; Me_4Si), δ: 14.10–13.05 (1H, br s, N*H*). ^{13}C NMR (125 MHz; DMSO-d_6; Me_4Si), δ: 160.8 (s), 138.7 (br m), 120.0 (br q, ^1J(CF) = 270.5 Hz), 113.2 (br s). ^{19}F NMR (376 MHz; DMSO-d_6; $CFCl_3$), δ: −62.04 (br s, CF_3). MS (*m*/*z*): 248 (M^+). Anal. Calcd for $C_6H_2F_6N_2O_2$: C, 29.05; H, 0.81; N, 11.29. Found: C, 28.87; H, 1.11; N, 11.02.

3,4,5-Tris(trifluoromethyl)pyrazole (5). A mixture of acid **11** (11.6 g, 46 mmol), SF_4 (14.9 g, 138 mmol), and HF (2 mL) was heated at 100 °C for 5 h in a stainless still autoclave (100 mL total volume). After the mixture was cooled to room temperature, gaseous products were vented off and the mixture was treated with water (100 mL). The product was filtered off and was crystallized from hexane (300 mL) to give pure pyrazole **5** (10.2 g, 38 mmol, 80% yield) as a semihydrate. Mp: 82–83 °C (lit.[24] mp 49–53 °C). Crystals of compound **5**, suitable for an X-ray diffraction study were obtained by a slow evaporation of a diluted solution of **5** in hexane. ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si), δ: 12.01 (1H, broad s, N*H*). ^{13}C NMR (125 MHz; $CDCl_3$; Me_4Si), δ: 138.1 (br s), 119.8 (q, ^1J(CF) = 268.8 Hz), 118.6 (q, ^1J(CF) = 271.0 Hz), 111.2 (q, ^2J(CF) = 42.3 Hz). ^{19}F NMR (470 MHz; $CDCl_3$; $CFCl_3$), δ: −55.92 (m, CF_3), −51.12 (br s, CF_3). MS (*m*/*z*): 204 (M^+). Anal. Calcd for $C_6HF_9N_2{\cdot}0.5H_2O$: C, 25.64; H, 0.72; N, 9.97. Found: C, 26.53; H, 0.51; N, 9.80.

X-ray Diffraction Study. The crystals of pyrazole **4** ($C_5H_2F_6N_2$) are monoclinic. At 100 K, a = 16.4630(5) Å, b = 12.5288(3) Å, c = 21.5826(6) Å, β = 111.568(3)°, V = 4140.0(2) Å^3, M_r = 204.09, Z = 24, space group $P2_1/n$, d_{calc}= 1.965 g/cm^3, μ(Mo Kα) = 0.236 mm^{-1}, F(000) = 2400. Intensities of 37785 reflections (11978 independent, R_{int} = 0.050) were measured on the Xcalibur-3 diffractometer (graphite-monochromated Mo Kα radiation, CCD detector, ω-scanning, $2\Theta_{max}$ = 60°).

The crystals of pyrazole **5** (2 $C_6HF_9N_2{\cdot}H_2O$) are triclinic. At 100 K, a = 9.0544(5) Å, b = 9.4420(6) Å, c = 11.9252(8) Å, α = 92.914(5)°, β = 101.077(5)°, γ = 108.534(5)°, V = 941.7(1) Å^3, M_r = 562.19, Z = 2, space group $P\bar{1}$, d_{calc}= 1.983 g/cm^3, μ(Mo Kα) = 0.250 mm^{-1}, F(000) = 548. Intensities of 11071 reflections (5488 independent, R_{int} = 0.027) were measured on the Xcalibur-3 diffractometer (graphite monochromated Mo Kα radiation, CCD detector, ω-scanning, $2\Theta_{max}$ = 60°).

The structures were solved by direct methods using the SHELXTL package.[46] The position of the hydrogen atoms was located from electron density difference maps and refined by the "riding" model with U_{iso} = nU_{eq} (n = 1.5 for the water molecule and n = 1.2 for other hydrogen atoms) of the carrier atom for the structure **5** and within isotropic approximation for the structure **4**. Full-matrix least-squares refinement against F^2 in anisotropic approximation for non-hydrogen atoms using 11951 (**4**), 5457 (**5**) reflections was converged to: wR_2 = 0.120 (R_1 = 0.050 for 6968 reflections with $F > 4\sigma(F)$, S = 0.984) for structure **4** and wR_2 = 0.093 (R_1 = 0.040 for 2953 reflections with $F > 4\sigma$(F), S = 0.814) for structure **5**. The final atomic coordinates, and crystallographic data for molecules **4** and **5** have been deposited to with the Cambridge Crystallographic Data Centre, 12 Union Road, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk) and are available on request quoting the deposition numbers CCDC 834871 for **4** and CCDC 782780 for **5**).

■ ASSOCIATED CONTENT

Supporting Information

Full spectroscopic data for all new compounds. Determination of pK_a values and fluorescence measurements for pyrazoles **4** and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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