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Filling the gap: Chemistry of 3,5-bis(trifluoromethyl)-1*H*-pyrazoles

Angelo Maspero [a,*], Giovanni B. Giovenzana [b], Damiano Monticelli [a], Silvia Tagliapietra [c], Giovanni Palmisano [a], Andrea Penoni [a]

[a] Dipartimento di Scienza e Alta Tecnologia, Università degli Studi dell'Insubria, Via Valleggio 11, I-22100 Como, Italy
[b] Dipartimento di Scienze del Farmaco, Università degli Studi del Piemonte Orientale "A. Avogadro", Largo Donegani 2/3, I-28100 Novara, Italy
[c] Dipartimento di Scienza e Tecnologia del Farmaco, Università degli Studi di Torino, Via Giuria 9, I-10125 Torino, Italy

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ABSTRACT

Pyrazoles represent important building blocks for the preparation of bioactive compounds and a large variety of materials, due to their rich coordination chemistry. Unusual and interesting properties may be imparted to molecules embodying highly fluorinated pyrazoles, but to date only few examples of polyfluorinated pyrazoles have been described. In this work we report an improved preparation of 3,5-bis(trifluoromethyl)-1*H*-pyrazole, the subsequent transformation into hitherto unknown 4-functionalized (F, Cl, Br, I, NO_2, NH_2) derivatives and the evaluation of selected chemical and physical properties of these compounds.

1. Introduction

It is well known that the presence of a C–F bond (as alkyl/aryl-F or CF_3, SCF_3 and OCF_3 functional groups) in an organic framework can dramatically modify the physicochemical profile including, i.a., increased chemical and metabolic stability (by blocking oxidative metabolism), enhanced lipophilicity, conformational changes, low dielectric constant, changes in hydrogen bonding ability (i.e., a good hydrogen-bond acceptor) [1]. In this context, the CF_3 group represents one of the most powerful electron-withdrawing groups as documented by the various Hammett σ values [σ_m, 0.42;σ_p, 0.54; σ_m^+ 0.52; σ_p^+, 0.61; σ_I, 0.38; σ_R 0.18] [2]. The electronic effect of CF_3 combined to its relatively small steric effect makes this group an interesting structural motif for the design of pharmaceuticals, agrochemicals and functional materials (e.g., polymers and liquid crystals). In particular, the last years have witnessed a blooming of research interest on the preparation, characterization and optimization of porous functional materials based on metal ions linked by organic spacers (as carboxylate, pyrazolate or triazolate ligands) in 3D-networks [i.e., metal organic frameworks (MOFs)] with the aim of obtaining outperforming adsorbents for environmentally relevant gases [3]. As anticipated, it has been shown that fluorinated MOFs (F-MOFs) wherein hydrogen atoms are substituted by fluorine atoms leads to enhanced thermal stability and low surface tension [4]. While fluorinated carboxylates has been well-documented, the literature contains no detailed reports of synthesis of highly fluorinated pyrazoles that might provide potential leads in the formation of F-MOFs. Our abiding interest in pyrazolates as ligands in coordination and organometallic chemistry [5] prompted to optimize the access to 3,5-bis(trifluoromethyl)-1*H*-pyrazole **2** and to develop methodology for further elaboration to its derivatives **3**–**8**, thereby filling this gap [6]. Within this context, papers by Trofimenko [7] and Elguero [8] are today recognized as the seminal works, both theoretical and experimental, to the chemistry of pyrazoles.

2. Results and discussion

The primary problem affecting any methods targeting 3,5-bis(trifluoromethyl)-1*H*-pyrazole **2** in large supply is poor recovery due to volatility loss (i.e., vapour pressure 626.6 Pa @ STP conditions). Preparation of **3** was achieved through adaptation of the procedure of Venanzi [9] and based on a two-step cyclocondensation of the appropriate β-dicarbonyl compound with hydrazine. In the event, this involved the addition of neat hydrazine hydrate to a 1 M solution of hexafluoroacetylacetone (hfacac) **1a** in EtOH at 5 °C, followed by refluxing for 8 h and subsequent removal of the solvent at 40 °C. The unusual stability of the intermediate half-aminals (i.e., hydroxypyrazolines and dihydroxypyrazolidines) [10] represents the major kinetic bottleneck [11], thereby limiting the performance of such approach en route to **2** (Scheme 1). This was readily overcome by acid treatment (98% H_2SO_4, 0 °C followed by quenching in ice, our procedure). In spite of extraordinary volatility [12], this route gave the required **2** in reproducible yield ranging from 79% to 88% and could be readily scaled up to produce quantities of **2** in excess of 20 g. Also, it must

* Corresponding author. Tel.: +39 0 31 2386472; fax: +39 0 31 2386449.
E-mail address: angelo.maspero@uninsubria.it (A. Maspero).

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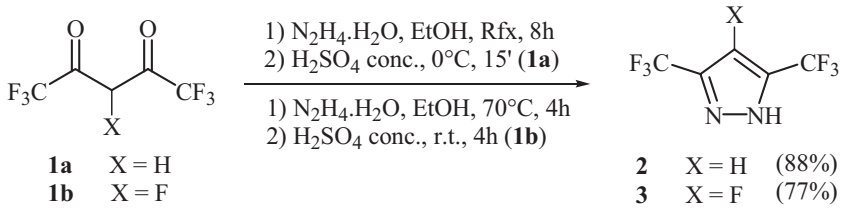


Scheme 1.

be noted that meticulous adherence to experimental details by Venanzi (i.e., thermal dehydration at 180 °C) is essential in order to obtain maximum yields, but in our hands this procedure led to **2** in erratic yields (30–60%).

Furthermore, aprotic conditions (anhydrous hydrazine, Hünig's base, 3 Å molecular sieves in refluxing toluene) were employed throughout to avoid half-aminal formation leading to **2** in 40% (unoptimized) yield; however, the difficulty in handling of anhydrous N_2H_4 have curtailed the utility of this method.

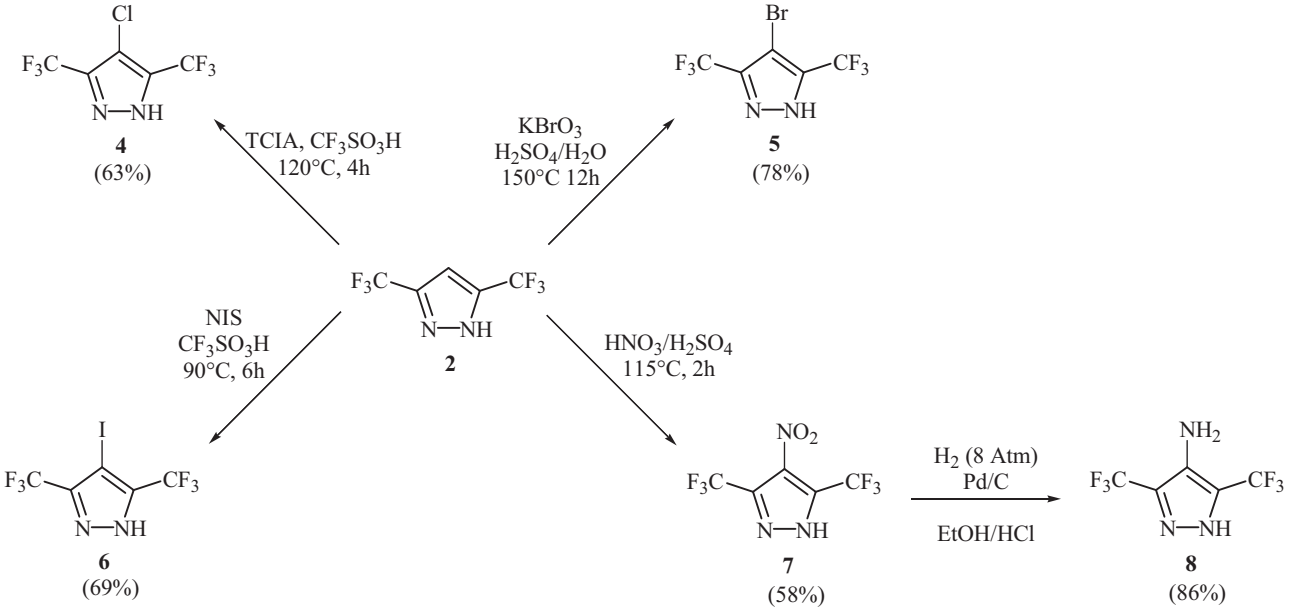
With an easy access to an ample supply of **2** [13], our attention was next focused on the reactivity towards electrophilic species although it was expected that the presence of two CF_3 groups would deeply impact the electronic and steric properties of pyrazole ring. For the sake of comparison, trifluoromethyl benzene undergoes nitration 40,000× more slowly than benzene [14]! Accordingly, **2** is required to withstand harsh conditions but care must be exercised in view of the well-known propensity of CF_3 group located on (hetero)aromatic ring systems to undergo hydrolysis to CO_2H functionality by action of strong protic acids and high temperatures [15].

The first efforts towards the functionalization of **2** (Scheme 2) were devoted to halogenation reactions. The presence of an halogen atom more significantly would allow for further elaboration either by Pd-catalyzed Suzuki-Miyaura and Sonogashira cross-coupling or nucleophilic substitution to give more diversified derivatives.

Different conditions were explored in order to achieve an efficient chlorination of the pyrazole ring of compound **2**. Initial attempts relied on *N*-chloroimides [*N*-chlorosuccimide (NCS), *N*-chlorobenzotriazole (NCBt), trichloroisocyanuric acid (TCIA)] as chlorine carrier but **2** was left practically unchanged in EtOAc or DMF even after prolonged treatment at room temperature under ultrasound irradiation and in the presence of catalysts. Instead, prolonged heating (at 80 °C) of **2** with NCS alone in DMF led to 55% conversion (checked by GC–MS), topping after 22 h. Compound **4** was difficult to purify due to either detrimental presence of DMF during workup or retention of succinimide in the crude product, thus resulting in yields of less than 30% [16].

Recourse to superelectrophilic reagents, which proved to be particularly conducive to clean halogenation of deactivated substrates was made. However, exposure of **2** to NCS in 98% H_2SO_4 at 120 °C for 6 h resulted in low conversion (20%) whereas changing to CF_3SO_3H (triflic acid) (80 °C, 6 h) brought to extensive decomposition of NCS and no chlorinated pyrazoles were observed at all. The successful conversion of **2**–**4** was realized by making use of a different chlorine carrier in the presence of a Brønsted acid. After additional experimentation, we found that when **2** was subjected to trichoroisocyanuric acid (TCIA) in CF_3SO_3H [17] at 120 °C for 4 h, the required **4** was finally obtained. Separation of **4** from byproducts was simpler, thereby allowing to reach an isolated yield of 63%. Multigram quantities (3–6 g) of **4** were routinely prepared using these reaction conditions. Interestingly, the reaction proceeded cleanly in triflic acid (i.e., a superacidic Brønsted acid with H_0 – 14.1 vs. 11.9 for 100% H_2SO_4) [18]. Regardless the reaction conditions, the use of TCIA in 98% H_2SO_4 or in FSO_3H (H_0 – 15.1) gave a mixture of **4** and 3,5-bis(trifluoromethyl)-4-pyrazolesulfonic acid or messy results. Although triflic acid is 10 times weaker than fluorosulfonic acid it avoids sulfonation or oxidation as side reactions.

N-Bromosuccinimide (NBS) was at first selected as brominating agents. Indeed, heating **2** with NBS in DMF at 130 °C for 16 h



Scheme 2.

provided a clean bromination to **5** as observed by GC–MS. Nevertheless, the same problems previously observed in the removal of succinimide from the chloro pyrazole spoiled the workup procedure, reducing once more the isolated yields to 43%. Reaction of **2** with other brominating agents (e.g., *N*,*N*′-dibromo-5,5-dimethylhydantoin, benzyltrimethylammonium tribromide, dibromoisocyanuric acid) in the presence of a Brønsted acid (triflic acid, 98% H_2SO_4) failed to provide **5** in satisfactory yields while we were able to obtain **5** (78% isolated yield) employing $KBrO_3$ in 98% H_2SO_4 at 150 °C for 12 h [19].

Iodination usually requires stronger activating conditions in order to generate a reactive electrophilic iodonium species. A thorough examination of literature procedures for iodination of deactivated (hetero)aromatic systems indicated that superelectrophilic iodine (I) salts (by productive merger of iodine carrier and protic acids) would represent the method of choice. The first attempts were performed with molecular iodine in 20% oleum (H_0 – 13.41) at 160 °C for 10 h in a sealed vessel but this route was clearly disfavored by the low yield of **6** (32%) due to the anticipated competitive sulfonation and/or hydrolysis of **2**. After several variations in reaction conditions, exposure to *N*-iodosuccinimide in triflic acid at 90 °C for 6 h led to **5** in a satisfying 69% yield avoiding the formation of byproducts [20]. This different behaviour may be most explained by the different solubilities of the reaction products. Whereas **6** precipitates directly by aqueous work-up, the corresponding halo derivatives issuing from chlorination and bromination are likely to be more soluble in the aqueous reaction mixture.

With **4** in hand, we proceeded to investigate nucleophilic displacement of chlorine by fluoride [HalEx (halogen exchange) or Finkelstein reaction] [21] to produce the perfluorinated pyrazole **3**. However, despite examining a range of fluoride sources (CsF, spray dried KF, NaF), solvents (MeCN, DMF, DMSO, sulfolane), reaction times, temperatures and additives (e.g., cetyltrimethylammonium bromide, tetraphenylphosphonium bromide, Kryptofix® 222), we were unable to effect clean reaction of chloro derivative **4**. The preparation of **3** was then achieved relying on the commercial availability of 1,1,1,3,5,5,5-heptafluoro-2,4-pentanedione **1b** [22]. The same conditions employed in the preparation of the 4-unsubstituted pyrazole **2** were applied leading to the isolation of the heptafluoropyrazole **3** in 77% yield.

Additional experiments were projected towards the introduction of nitrogen-containing functional groups. Initial efforts towards the nitration of **2** using KNO_3 and 98% sulfuric acid failed giving only recovered starting material. Accordingly, it is stated authoritatively by Elguero et al. [23] that 3,5-bis(trifluoromethyl)-1H-pyrazole **2** cannot be nitrated at the 4-position. However, in our hands, use of 98% H_2SO_4 – fuming HNO_3 in 2:1 molar ratio (at 115 °C) gave complete consumption of the starting material after 18 h and the desired product **7** [24] was obtained in an isolated yield of 58%. The presence of a nitro group in **7** provided the opportunity for further elaboration. Thus, a variety of reagents and conditions for the reduction of the nitro group were screened [e.g., H_2 (101 kPa), 10% Pd/C in EtOH; $SnCl_2{\cdot}2H_2O$ in EtOH; N_2H_4 or HCO_2NH_4 in the presence of Pd/C; $Na_2S_2O_4$, K_2CO_3 in CH_2Cl_2 under PTC conditions] but all these conditions led to intractable mixtures. For the majority of reductions, notable side-reactions were the formation of azo- and azoxy derivatives (checked by ESI-MS) arising from incomplete reduction and/or oxidation process. Lastly, conversion of the nitro derivative **7**–**8** was best carried out by catalytic hydrogenation (at 810 kPa) in a 4:1 EtOH–12 N HCl mixture over 10% Pd/C at ambient temperature for 18 h delivering the desired amino compound **8** in 86% yield. This compound rapidly turned purple on standing in air and was kept at −15 °C under nitrogen.

The synthesized 3,5-bis(trifluoromethyl)-1*H*-pyrazoles **3**–**8** were fully characterized by IR, UV, pK_a (pzH/pz$^-$), ^{1}H, ^{13}C, ^{19}F NMR, GC–MS and elemental analysis confirming their structure and purity.

3. Conclusion

An optimized protocol for the preparation of 3,5-bis(trifluoromethyl)-1*H*-pyrazole **2** was developed. Contrary to the original assumptions and after a fine tuning of experimental conditions, the electrophilic substitution of **2** was successfully achieved. The obtained 4-substituted derivatives **3**–**8** appear to be valuable synthetic intermediates for preparation of heterocyclic compounds of pharmaceutical interest, thereby expanding the already burgeoning arsenal of polyfluorinated pyrazoles. Furthermore, these new compounds pave the route to designing and tailoring more complex structures that can be used to suit a well-defined molecular function.

4. Experimental

4.1. General techniques

Chemicals were used as received (Sigma Aldrich). Infrared spectra (nujol) were recorded on a Shimadzu Prestige-21 FTIR instrument. Elemental analyses were carried out on a Perkin Elmer CHN Analyzer 2400 Series. Melting points were determined on a Stuart Scientific SMP3 melting point apparatus. Unless stated otherwise ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 400 spectrometers in DMSO-d_6 using TMS as an internal standard. Unless stated otherwise ^{19}F NMR spectra were recorded on a Jeol Eclipse ECP300 (282.3 MHz) in $CDCl_3$ and referenced to $CFCl_3$ using an external standard of $BF_3{\cdot}OEt_2$ ($\delta = -153.0$ ppm). GC–MS analyses (retention times t_R are reported) and mass spectra were determined with a Thermo Quest GC with a Agilent DB-5MS capillary column (30 m, 0.25 mm) equipped with a Ultra Trace MS mass selective detector under the following conditions: 5 min @ 50 °C, 50–150 °C @ 5°/min, 150–280 °C @ 15 °C/min, 15 min @ 280 °C; helium gas flow 1 mL/min. Elemental analyses were performed in-house at the Dipartimento di Scienza e Alta Tecnologia with a Perkin Elmer 2400 Series II Elemental Analyzer. In general, samples prepared for CHN analyses were dried in vacuum (1600 Pa) over P_4O_{10} for 18 h at ambient temperature. The pK_a (pzH/pz$^-$) were determined at 20 °C in aqueous 0.1 M KNO_3 by neutralization titrations with 0.02 M NaOH using a pHmeter model GLP 21 (Crison Strumenti Spa, Italy) and a glass electrode model 50 11 T (Crison Strumenti Spa, Italy) embodying a temperature sensor. Repetitive measurements ($n = 3$) suggested that the method precision is ±0.02 expressed as standard deviation. Spectra (EtOH) in the ultraviolet region (190–350 nm range) were measured by a Beckman DU-640 spectrophotometer (Beckman, USA). Thermogravimetric and differential (TGA-TDA) analysis was performed with a NETZSCH STA 409 thermobalance. Pressure reactions were carried out in autoclave. Yields refer to isolated compounds estimated to be >95% pure as determined by capillary GC analysis.

4.2. Preparation of pyrazoles 2–8

4.2.1. 3,5-Bis(trifluoromethyl)-1H-pyrazole (2)

A 250-mL three-necked round-bottomed flask, equipped with a magnetic stitrring bar, thermometer, water condenser and dropping funnel was loaded with hexafluoroacetylacetone **1a** (29.4 g, 20 mL; 141 mmol) and EtOH (100 mL). The flask was cooled to 5 °C with an ice bath. Hydrazine monohydrate (7.0 g, 6.8 mL; 140 mmol) was added over 20 min, while keeping the reaction temperature below 8 °C. After addition was complete, the

mixture was brought to reflux for 8 h. After cooling to room temperature, the reaction mixture was evaporated on a rotary evaporator while keeping the bath temperature below 40 °C to leave a yellow syrup. This was dissolved in 98% H_2SO_4 (10 mL) under ice cooling and vigorous stirring. After 15 min the reaction mixture was cautiously poured onto ice (300 g) and the light yellow solid was collected, washed with ice-cold water (50 mL) to afford the title compound **2** (25.13 g; 88%) as a colourless solid with a distinctive odor. ^{1}H NMR (DMSO-d_6/$CDCl_3$, 2:1): δ = 5.70 (brs, 1H, NH), 7.40 (s, 1H, H-4). ^{13}C NMR: δ = 138.1 (q, $^2J_{C-F}$ = 39 Hz, C-3/C-5), 120.5 (q, $^1J_{C-F}$ = 267 Hz, CF_3), 105.2 (s, C-4). ^{19}F NMR (DMSO-d_6/$CDCl_3$, 2:1): δ = −62.5 (s). IR: 3160 (s) 1510, 1595 (s) 1150 (s) cm^{-1}. GC MS (t_R 6.78 min). Anal. Calcd for $C_5H_2F_6N_2$: C, 29.43; N, 13.73. Found: C, 29.44; N, 13.76. pK_a 7.10 [Ref. [25] 7.5]. Mp 81 °C [Ref. [25] 83–84 °C]. The sample purity of **2** was determined to be >98% by DSC (scan rate, 2.5 °C/min; mp 85.2 °C).

4.2.2. 4-Chloro-3,5-bis(trifluoromethyl)-1H-pyrazole (4)

Trichloroisocyanuric acid (TCIA) (2.32 g, 10 mmol) was added portionwise over 10 min to triflic acid (6 mL) chilled to 0 °C. Pyrazole **2** (2.04 g, 10 mmol) was added and allowed to warm to room temperature as it stirred for 5 min. The reaction temperature was brought to 120 °C and stirred for further 5 h, while following the conversion by GLC. The colourless mixture was cooled at 0 °C, poured into water/ice (10 mL), extracted with CH_2Cl_2 (4 × 20 mL) and dried over Na_2SO_4. Evaporation of the solvent afforded the title compound **4** (1.50 g; 63%) as an off- white solid. ^{13}C NMR: δ = 135.7 (q, $^2J_{C-F}$ = 39 Hz, C-3/C-5), 119.4 (q, $^1J_{C-F}$ = 268 Hz, CF_3), 109.5 (s, C-4). ^{19}F NMR: δ = –61.8 (s). IR: 3198 (s), 1577 (w), 1326 (s), 1273 (s), 1212 (vs), 1164 (vs), 973 (s) cm^{-1}. UV (EtOH): λ_{max} (log ε) = 224 nm (3.25). GC MS: (t_R 13.15 min). Anal. Calcd for $C_5HClF_6N_2$: C, 25.18; N, 11.74. Found: C, 25.15; N, 11.71. pK_a 5.49. Mp 89 °C.

4.2.3. 4-Bromo-3,5-bis(trifluoromethyl)-1H-pyrazole (5)

Method A. Pyrazole **2** (2.04 g, 10 mmol) was dissolved in DMF (5 mL) and under stirring *N*-bromosuccinimide (NBS) (2.31 g, 13 mmol) was added at room temperature. The solution was warmed at 130 °C for 15 h, cooled to room temperature, and water (200 mL) was added, the mixture was then extracted with ethyl acetate (4 × 30 mL). The organic layers were washed with water, brine and dried over Na_2SO_4. The solvent was removed by vacuum at 40 °C and a colourless product was obtained. This was purified by sublimation under vacuum (1.33 Pa @ 80 °C) to give the title compound **5** (1.21 g; 43%).

Method B. A mixture of $KBrO_3$ (1.67 g, 10 mmol), pyrazole **2** (2.04 g; 10 mmol) and 98% H_2SO_4 (d 1.84 g/mL) (13 mL) was heated in 25-mL stainless steel Teflon-lined autoclave at 150 °C for 12 h. The mixture was allowed to cool to room temperature and poured slowly onto ice (100 g). The off-white product was collected by filtration, washed with ice-cold water (2 × 10 mL) and dried under vacuum at room temperature for 4 h to give the title compound (2.20 g; 78%).

^{13}C NMR: δ = 138.1 (q, $^2J_{C-F}$ = 38 Hz, C-3/C-5), 119.2 (q, $^1J_{C-F}$ = 269 Hz, CF_3), 92.6 (s, C-4). ^{19}F NMR: δ = −62.1 (s). IR: 3174(s), 1577 (s), 1395 (s), 1321 (s), 1261 (vs), 1200 (vs), 1141 (vs), 981 (s) cm^{-1}. UV (EtOH): λ_{max} (ε) = 225 nm (3.20). GC MS: (t_R 15.38 min). Anal. Calcd for $C_5HBrF_6N_2$: C, 21.22; N, 9.90. Found: C, 21.26; N, 9.83. pK_a 6.02. Mp 109 °C.

4.2.4. 4-Iodio-3,5-bis(trifluoromethyl)-1H-pyrazole (6)

Method A. A mixture of pyrazole **2** (1.02 g; 5 mmol), iodine (0.622 g, 2.58 mmol) and fuming H_2SO_4 (20% free SO_3 basis) (8.5 mL) was heated in a 25-mL stainless steel Teflon-lined autoclave at 160 °C for 10 h. The mixture was cooled to 0 °C and the excess of iodine was destroyed by the addition of a 0.1 M Na_2SO_3 solution. The white product was collected by filtration, washed with ice-cold water (3 × 5 mL) and dried under vacuum at room temperature for 4 h to afford the title compound **6** (530 mg; 32%).

Method B. *N*-Iodosuccinimide (NIS) (2.25 g; 5 mmol) was dissolved in triflic acid (10 mL) at 0 °C kept under stirring for 5 min (during which time a blue colour developed). Pyrazole **2** (1.02 g; 5 mmol) was then slowly added over 5 min. The mixture was warmed to 90 °C for 6 h, cooled to 0 °C and the deep blue solution was cautiously poured into ice (100 g). A white precipitate formed, which was collected by filtration, washed with ice-cold water (3 × 10 mL) and dried under vacuum for 4 h to leave the title compound **5** (1.14 g, 69%).

^{13}C NMR (DMSO-d_6): δ = 141.5 (q, $^2J_{C-F}$ = 38 Hz, C-3/C-5), 119.2 (q, $^1J_{C-F}$ = 269 Hz, CF_3), 55.7 (s, C-4). ^{19}F NMR: δ = −61.8 (s). IR: 3166(s), 1569 (w), 1310 (s), 1192 (vs), 1156 (vs), 997 (s) cm^{-1}. UV (EtOH): λ_{max} (ε) = 232 nm (3.04). GC MS: (t_R 18.84 min). Anal. Calcd for $C_5HF_6IN_2$: C, 18.20; N, 8.49. Found: C, 18.22; N, 8.58. pK_a 6.09. Mp 126 °C.

4.2.5. 4-Fluoro-3,5-bis(trifluoromethyl)-1H-pyrazole (3)

Hydrazine monohydrate (0.5 mL, 10.4 mmol) was slowly added to a solution of 1,1,1,3,5,5,5-heptafluoroaceylacetone **1b** (1.0 mL, 6.95 mmol) in EtOH (8 mL) at room temperature. The solution was then heated to 70 °C for 4 h. The solvent was removed by vacuum at 20 °C and to the yellow oil 98% H_2SO_4 (1 mL) was cautiously added under ice cooling and stirring. After 15 min the reaction mixture was cautiously poured onto ice (20 g), the solid was collected, washed with ice-cold water (5 mL) to afford the title compound **3** (1.04 g; 77%) as a colourless glass.

^{13}C NMR (CD_2Cl_2): δ = 118.8 (qd; $^1J_{C-F}$ = 267 Hz, $^3J_{C-F}$ 3 Hz; CF_3), 125.4 (qd; $^2J_{C-F}$ = 42 Hz, $^2J_{C-F}$ 13 Hz; C-3/C-5), 142.1 (s, $^1J_{C-F}$ = 265 Hz, C-4). ^{19}F NMR: δ = −60.4 (s,6F), −166.6 (s, 1F). GC MS: (t_R 8.42 min). Anal. Calcd for $C_5HF_7N_2$: C, 27.04; N, 12.61. Found: C, 27.09; N, 12.53. pK_a 6.85. Mp 51 °C (DSC).

4.2.6. 4-Nitro-3,5-bis(trifluoromethyl)-1H-pyrazole (7)

Fuming HNO_3 (d 1.50 g/mL, 3.5 mL) was added over 10 min to the ice-cooled solution of pyrazole **2** (2.04 g, 10 mmol) in 98% H_2SO_4 (d 1.80 g/mL, 8.1 mL). The solution was then transferred into a 25-mL stainless steel Teflon-lined autoclave, sealed and heated at 115 °C for 12 h. On cooling to 0 °C, the brown solution was cautiously poured into ice (100 g) and kept at 0 °C for 30 min. The white solid was then filtered off, washed with ice-cold water (2 × 10 mL) and dried under vacuum at room temperature for 4 h to give the title compound **7** (1.44 g; 58%).

^{13}C NMR (DMSO-d_6/$CDCl_3$, 2:1): δ = 134.9 (q, $^2J_{C-F}$ = 39 Hz, C-3/C-5), 130.2 (s, C-4), 119.2 (q, $^1J_{C-F}$ = 268 Hz, CF_3), 55.7 (s, C-4). ^{19}F NMR: δ = −61.8(s). IR: 3239 (s), 1553 (s), 1513 (s), 1264 (s), 1224 (s), 1200 (vs), 1155 (vs), 1131 (vs), 973 (vs) cm^{-1}. UV (EtOH): λ_{max} (log ε) = 225 nm (3.11). GC MS: (t_R 20.50 min). Anal. Calcd for $C_5HF_6N_3O_2$: C, 24.11; N, 16.87. Found: C, 24.08; N, 17.02. pK_a 3.39. Rf (silica) = 0.10 (EtOAc-hexane, 4:1). Mp 80 °C.

4.2.7. 4-Amino-3,5-bis(trifluoromethyl)-1H-pyrazole (8)

Into a 50-mL glass-lined autoclave were charged 4-nitro-3,5-bis(trifluoromethyl)-1*H*-pyrazole **7** (3.60 g, 14.5 mmol), 10% Pd/C (0.5 g) and 4:1 (v/v) EtOH–12 N HCl mixture (20 mL). The reactor was pressurized to 810 kPa with hydrogen and stirred at room temperature for 18 h. After venting, the mixture was filtered through a Celite® pad, rinsing the filter cake well with EtOH (2 × 15 mL). The volatiles were removed on the rotary evaporator to leave the title compound **8** (2.72 g; 86%) as a light yellow solid which was stored at −15 °C under nitrogen.

^{13}C NMR (DMSO-d_6/$CDCl_3$, 2:1): δ = 124.2 (q, $^2J_{C-F}$ = 39 Hz, C-3/C-5), 128.4 (s, C-4), 120.6 (q, $^1J_{C-F}$ = 266 Hz, CF_3). ^{19}F NMR:

δ = −61.2 (s). IR: 3429 (w), 3399 (w), 3152 (s), 1604 (s), 1336 (s), 1307 (s), 1292 (s), 1145 (vs), 978 (s) cm^{-1}. UV (EtOH): λ_{max} (log ε) = 250 nm (3.20). GC MS: (t_R 12.89 min). Anal. Calcd for $C_5H_3F_6N_3$: C, 27.41; N, 19.18. Found: C, 27.29; N, 19.11. pK_a 8.13. Rf (silica) = 0.72 (EtOAc-hexane, 4:1). Mp 131 °C.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jfluchem.2012.04.003.

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