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Synthesis of fluorinated indazoles through ANRORC-like rearrangement of 1,2,4-oxadiazoles with hydrazine

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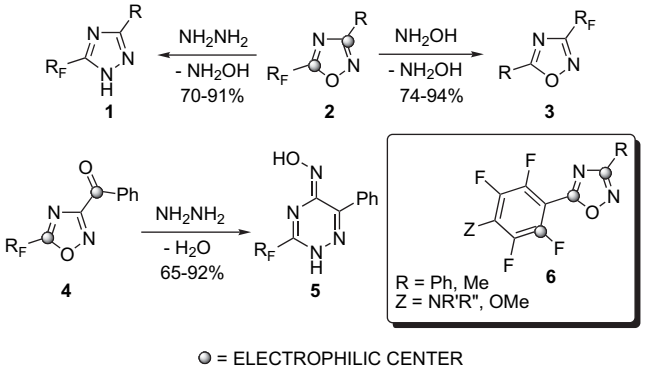
Abstract—A series of 6-substituted fluorinated indazoles has been obtained through an ANRORC-like rearrangement (Addition of Nucleophile, Ring-Opening and Ring-Closure) of 5-tetrafluorophenyl-1,2,4-oxadiazoles with hydrazine. The initial addition of the bidentate nucleophile to the electrophilic C(5) of the 1,2,4-oxadiazole ring, followed by ring opening and ring closure, leads to the formation of fluorinated indazoles in high yield under mild experimental conditions. Functionalization of the C(6) in the final indazole nucleus was preliminarily achieved through a nucleophilic aromatic substitution on the starting 5-pentafluorophenyl-1,2,4-oxadiazole.

1. Introduction

The synthesis of fluorinated heterocycles has generated much recent interest since these compounds have found useful applications in pharmaceuticals, agrochemicals and in materials science.[1,2] In general, the various approaches to achieve this goal include direct introduction of a fluorine or fluoroalkyl group, modification of functional groups, heterocyclization of open-chain fluorinated precursors and ring transformation of a suitable fluorinated heterocycle.[1,2]

For the latter approach, ANRORC-like rearrangements, which consist of the Addition of a Nucleophile followed by Ring-Opening and Ring-Closure steps, represent a very versatile strategy indeed.[3] This reaction pattern is well documented in the azine series,[3,4] but is quite rare in the case of five-membered heterocyclic derivatives.[3,5] In fact, only electron-poor azoles or systems bearing strongly electron-withdrawing groups present such reactivity.[3,5]

In this context, we have recently investigated the reactivity of 5-perfluoroalkyl-1,2,4-oxadiazoles **2** and **4** with bidentate nucleophiles such as hydrazine or hydroxylamine, and reported their ANRORC-like rearrangements into triazoles **1**,[6] 1,2,4-oxadiazole regioisomers **3**[7] or 1,2,4-triazinone oximes **5**[8] (Scheme 1).



Scheme 1.

In these reactions, 1,2,4-oxadiazole **2** reacted as a 1,3-dielectrophilic reagent; in fact, the presence of a strongly electron-withdrawing perfluorinated chain makes the C(5) (of the azole ring) a good electrophilic site, and allows the initial nucleophilic attack and ring-opening steps. The subsequent cyclization, involving the original C(3) of the azole nucleus, is driven by the formation of a more stable heterocyclic system.[6,7]

In 3-benzoyl-5-perfluoroalkyl-1,2,4-oxadiazoles **4**, the presence of a competing electrophilic centre in the side chain, partially changes the reactivity of the system, which is now identified as a 1,4-dielectrophile. The C(5) is still the preferred initial site of attack, while the final cyclization, involving the carbonyl linked at C(3) allowed the synthesis of fluorinated triazines **5** (Scheme 1).[8]

Keywords: 1,2,4-Oxadiazole; Indazole; Fluorinated heterocycles; ANRORC-like rearrangements.
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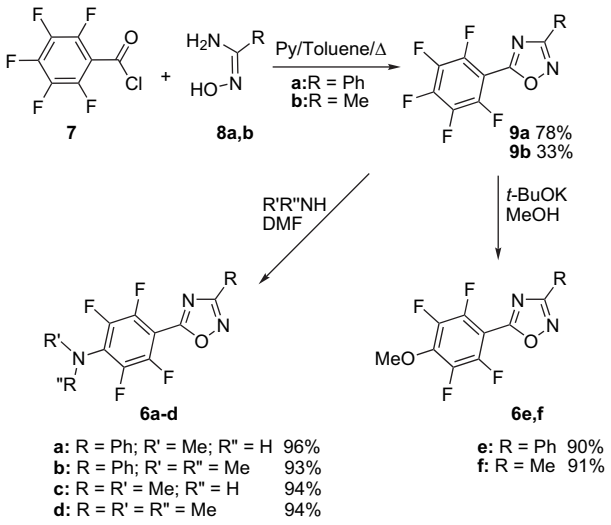
At this point, we became interested in verifying if the electrophilic behaviour of the azole C(5) could also be induced by fluorinated aryl substituents, and studied the reactivity of 5-tetrafluorophenyl-substituted 1,2,4-oxadiazoles **6** (Scheme 1) with hydrazine as a bidentate nucleophile.

2. Results and discussion

Pentafluorophenyl oxadiazoles **9** were prepared through the conventional amidoxime route, by reacting amidoximes **8a**,**b** and pentafluorobenzoyl chloride **7** in the presence of pyridine (Scheme 2).[9,10]

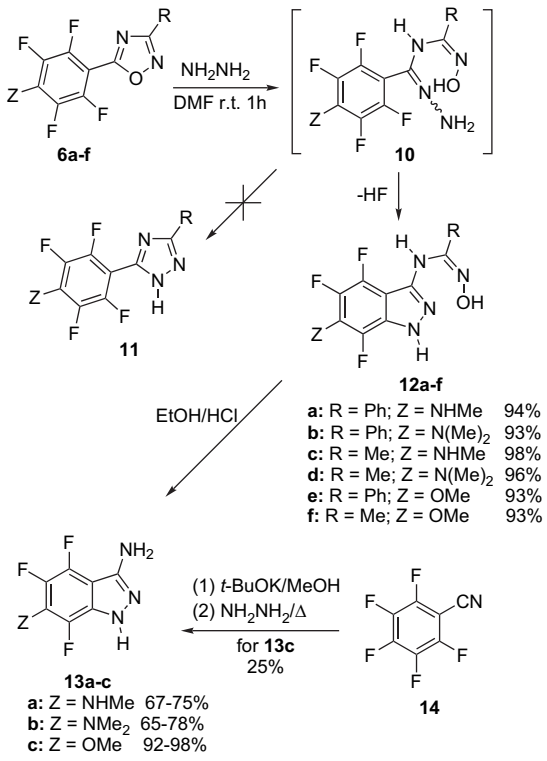


Scheme 2.

On the basis of previous results,[11] one can expect that the 4′-position of the pentafluorophenyl ring may easily undergo a nucleophilic aromatic substitution in the presence of a nucleophile, and this behaviour would interfere with the studied hydrazinolysis reaction.[12] Therefore we decided to preliminarily functionalize the fluorinated ring at its C(4) position by reaction with amines or methanol to obtain tetrafluorophenyl-1,2,4-oxadiazoles **6a–d** or **6e**,**f**, respectively (Scheme 2).

Surprisingly, the reaction of oxadiazoles **6a–f** with hydrazine in DMF at rt did not produce 1,2,4-triazoles **11**, which were expected as a result of an initial nucleophilic attack on the C(5) of the oxadiazole followed by a cyclization at the C(3) position.[6] The final cyclization step, instead, involves the side-chain electrophilic site located on the 2′-position of the fluorinated aromatic ring, and, by substitution of a fluorine atom through an intramolecular S_NAr, produced ring fluorinated 6-substituted *N*-indazolyl-amidoximes **12a–f** (Scheme 3) (yield range: 93–98%).

The structures of **12a–f** were confirmed by analytical and spectroscopic data (^{1}H NMR, ^{19}F NMR, IR and HRMS). Moreover, acidic hydrolysis of **12a–f** yielded the corresponding fluorinated 3-amino-indazoles **13**. For comparison, a sample of **13c** was also prepared, in a *one-pot* reaction, from pentafluorobenzonitrile **14** (Scheme 3).



Scheme 3.

The proposed mechanism considers the attack of the hydrazine onto the C(5) of the oxadiazole ring as the initial step, followed by the ring opening into **10** (the *Z*-configuration of the amidoxime was expected on the basis of preservation along the reaction process of the initial configuration present in the oxadiazole ring).[8] In fact, a possible alternative initial attack on the 2′-position of the fluorinated ring could be excluded since 2′-substitution was never observed in the presence of other nitrogen nucleophiles, under the same conditions, or with stronger nucleophiles such as methoxide anion.

On the other hand, once the open-chain intermediate **10** is obtained, the cyclization into the stable heteroaromatic system **12** constitutes the driving force for the displacement of a fluorine from the C(2) of the fluorinated ring, by nucleophilic attack of the β-nitrogen of the bidentate nucleophile.

It is our opinion that the observed selectivity, between the C(3) of the starting azole and the C(2) of the fluoroaryl ring, for the final cyclization steps is determined by the stability of the reaction products.[13,14]

The proposed mechanism is in agreement with classical methodology reported for the synthesis of indazoles, through the formation of a N(1)–C(7a) bond, by cyclization of *o*-halo-arylhydrazones with the elimination of halogenhydric acid.[15]

3. Conclusions

The title reaction, performed under mild conditions, resulted in excellent yields of the isolated products. This synthetic

protocol allowed the preparation of 6-substituted ring-fluorinated indazoles starting from easily accessible 1,2,4-oxadiazole precursors. This approach represents an interesting synthetic methodology for fluorinated indazoles, also considering that such compounds are present in many pharmaceutically important structures, with a broad range of activities, including antiinflammatory,[16] antitumor,[17] anti-HIV,[18] antimicrobial,[19] contraceptive[20] and as nNOS inhibitors.[21]

The reported results clearly show how ANRORC-like rearrangements of five-membered heterocycles can be considered as a versatile synthetic strategy for the synthesis of fluorinated heterocycles. Such an approach is not restricted to perfluoroalkylated substrates but can also be applied to polyfluoroarylated 1,2,4-oxadiazoles. Moreover, the leaving group ability of the fluorine atom in the C(2) position of the fluoroaryl ring allows the cyclization into benzofused systems.

4. Experimental

4.1. General methods and materials

Melting points were determined on a Reichart-Thermovar hot-stage apparatus and are uncorrected. IR spectra (Nujol) were determined with a Shimadzu FTIR-8300 instrument; ^{1}H NMR spectra were recorded on a BRUKER AC 250 E spectrometer with TMS as an internal standard; ^{19}F NMR spectra were recorded on a BRUKER AVANCE 300 spectrometer with $CFCl_3$ as an internal standard. GC–MS determinations were carried out on a VARIAN STAR 3400 CX/SATURN 2000 system. Flash chromatography was performed by using silica gel (Merck, 0.040–0.063 mm) and mixtures of ethyl acetate and light petroleum (fraction boiling in the range of 40–60 °C) in various ratios. Compound **9a** was prepared in 78% as previously reported.[9]

4.2. Synthesis of 3-methyl-5-pentafluorophenyl-1,2,4-oxadiazole 9b

A mixture of acetamidoxime **8b** (0.74 g; 10 mmol), pyridine (0.9 mL; 11 mmol) and pentafluorobenzoyl chloride **7** (2.54 g, 11 mmol) in anhydrous toluene (100 mL) was refluxed for 4 h. After removal of the solvent, the residue was treated with water (100 mL) and then extracted with EtOAc (3×100 mL). The combined organic layers were dried over Na_2SO_4 and evaporated. Chromatography of the residue gave 1,2,4-oxadiazole **9b** (0.82 g, 33%): mp 41–42 °C (white crystals from EtOAc); ^{1}H NMR ($CDCl_3$) δ 2.55 (s, 3H); MS *m/z* 250 (M^+, 100); IR (Nujol) 1655 cm^{-1}. Anal. Calcd for $C_9H_3F_5N_2O$: C, 43.22; H, 1.21; N, 11.20. Found: C, 43.30; H, 1.20; N, 11.40.

4.3. Reaction of 5-pentafluorophenyl-1,2,4-oxadiazoles 9a,b with amines in DMF. General procedure

To a mixture of 5-pentafluorophenyl-1,2,4-oxadiazole **9** (1 mmol) in dry DMF (2 mL), the appropriate amine (1.1 mmol) was slowly added. After stirring for 3 h at rt, the mixture was diluted with water (50 mL) and the formed precipitate filtered and re-crystallized from an appropriate solvent, giving **6a–d**.

4.3.1. 5-[2,3,5,6-Tetrafluoro-4-(*N*-methylamino)-phenyl]-3-phenyl-1,2,4-oxadiazole 6a. Yield: 0.31 g, 96%, mp 160–163 °C (white crystals from H_2O/EtOH); ^{1}H NMR (acetone-d_6) δ 3.18–3.26 (m, 3H), 6.26 (s, 1H, exch. D_2O), 7.53–7.64 (m, 3H), 8.10–8.17 (m, 2H); ^{19}F NMR (acetone-d_6) δ −144.34 (br d, 2F, J=15.3 Hz), −167.28 (br d, 2F, J=17.1 Hz); MS *m/z* 323 (M^+, 100); IR (Nujol) 3435, 3380, 1690 cm^{-1}. Anal. Calcd for $C_{15}H_9F_4N_3O$: C, 55.73; H, 2.81; N, 13.00. Found: C, 55.70; H, 2.90; N, 12.90.

4.3.2. 5-[2,3,5,6-Tetrafluoro-4-(*N*,*N*-dimethylamino)-phenyl]-3-phenyl-1,2,4-oxadiazole 6b. Yield: 0.31 g, 93%, mp 120–122 °C (white crystals from EtOAc); ^{1}H NMR ($CDCl_3$) δ 3.14 (t, 6H, J_{H-F}=2.7 Hz), 7.50–7.55 (m, 3H), 8.17–8.20 (m, 2H); ^{19}F NMR ($CDCl_3$) δ −138.71 (br d, 2F, J=18.0 Hz), −152.91 (br d, 2F, J=17.1 Hz); MS *m/z* 337 (M^+, 100); IR (Nujol) 1645 cm^{-1}. Anal. Calcd for $C_{16}H_{11}F_4N_3O$: C, 56.98; H, 3.29; N, 12.46. Found: C, 57.00; H, 3.30; N, 12.40.

4.3.3. 5-[2,3,5,6-Tetrafluoro-4-(*N*-methylamino)-phenyl]-3-methyl-1,2,4-oxadiazole 6c. Yield: 0.25 g, 94%, mp 182–184 °C (white crystals from H_2O/EtOH); ^{1}H NMR (DMSO-d_6) δ 2.47 (s, 3H), 3.11–3.14 (m, 3H); 7.06 (s, 1H, exch. D_2O); ^{19}F NMR (DMSO-d_6) δ −132.82 (br d, 2F, J=15.9 Hz), −154.65 (br d, 2F, J=15.9 Hz); MS *m/z* 261 (M^+, 100); IR (Nujol) 3321, 3163, 1653 cm^{-1}. Anal. Calcd for $C_{10}H_7F_4N_3O$: C, 45.99; H, 2.70; N, 16.09. Found: C, 46.10; H, 2.60; N, 16.00.

4.3.4. 5-[2,3,5,6-Tetrafluoro-4-(*N*,*N*-dimethylamino)-phenyl]-3-methyl-1,2,4-oxadiazole 6d. Yield: 0.26 g, 94%, mp 71–74 °C (white crystals from EtOAc); ^{1}H NMR ($CDCl_3$) δ 2.52 (s, 3H), 3.12 (t, 6H, J_{H-F}=2.7 Hz); ^{19}F NMR ($CDCl_3$) δ −139.42 (br d, 2F, J=18.9 Hz), −153.24 (br d, 2F, J=17.7 Hz); MS *m/z* 275 (M^+, 100); IR (Nujol) 1647 cm^{-1}. Anal. Calcd for $C_{11}H_9F_4N_3O$: C, 48.01; H, 3.30; N, 15.27. Found: C, 48.10; H, 3.30; N, 15.30.

4.4. Reaction of 5-pentafluorophenyl-1,2,4-oxadiazoles 9a,b with methanol. General procedure

Oxadiazole **9** (1 mmol) was dissolved in a solution of *t*-BuOK (1.2 mmol) in dry MeOH (20 mL). After stirring for 24 h at rt, the solvent was evaporated, the residue treated with water (100 mL), filtered and crystallized from an appropriate solvent, giving 5-(2,3,5,6-tetrafluoro-4-methoxyphenyl)-1,2,4-oxadiazoles **6e**,**f**.

4.4.1. 5-(2,3,5,6-Tetrafluoro-4-methoxy-phenyl)-3-phenyl-1,2,4-oxadiazole 6e. Yield: 0.29 g, 90%, mp 103–104 °C (white crystals from H_2O/EtOH); ^{1}H NMR ($CDCl_3$) δ 4.25 (t, 3H, J_{H-F}=2.1 Hz), 7.49–7.56 (m, 3H), 8.17–8.21 (m, 2H); ^{19}F NMR ($CDCl_3$) δ −137.32 (br d, 2F, J=19.5 Hz), −157.43 (br d, 2F, J=17.1 Hz); MS *m/z* 324 (M^+, 100); IR (Nujol) 1683 cm^{-1}. Anal. Calcd for $C_{15}H_8F_4N_2O_2$: C, 55.57; H, 2.49; N, 8.64. Found: C, 55.60; H, 2.50; N, 8.60.

4.4.2. 5-(2,3,5,6-Tetrafluoro-4-methoxy-phenyl)-3-methyl-1,2,4-oxadiazole 6f. Yield: 0.24 g, 91%, mp 42–43 °C (white crystals from H_2O/EtOH); ^{1}H NMR ($CDCl_3$)

δ 2.54 (s, 3H), 4.24 (t, 3H, J_{H-F}=2.0 Hz); ^{19}F NMR ($CDCl_3$) δ −137.63 (br d, 2F, J=19.2 Hz), −157.33 (br d, 2F, J=20.7 Hz); MS *m/z* 262 (M^+, 100); IR (Nujol) 1653 cm^{-1}. Anal. Calcd for $C_{10}H_6F_4N_2O_2$: C, 45.81; H, 2.31; N, 10.69. Found: C, 45.70; H, 2.30; N, 10.80.

4.5. Reaction of 5-tetrafluorophenyl-1,2,4-oxadiazoles 6a–f with hydrazine in DMF. General procedure

To a mixture of oxadiazoles **6a–f** (1 mmol) in dry DMF (2 mL), an excess of hydrazine monohydrate (0.25 g, 5 mmol) was slowly added. After stirring for 3 h at rt, the mixture was diluted with 1 M HCl (50 mL) and the formed precipitate filtered. Re-crystallization of the residue from H_2O/EtOH (1:1) gave the corresponding (*Z*)-*N*-(4,5,7-trifluoro-*1H*-indazol-3-yl)-*N′*-hydroxy-amidine **12**.

4.5.1. (*Z*)-*N*-[4,5,7-Trifluoro-6-(*N*-methylamino)-1*H*-indazol-3-yl]-*N′*-hydroxy-benzamidine 12a. Yield: 0.31 g, 94%, mp 190–193 °C (white crystals from H_2O/EtOH); ^{1}H NMR (DMSO-d_6) δ 3.01 (s, 3H), 5.66 (s, 1H, exch. D_2O), 7.28 (br s, 3H), 7.36 (br s, 2H), 8.22 (s, 1H, exch. D_2O), 10.49 (s, 1H, exch. D_2O), 12.64 (s, 1H, exch. D_2O); ^{19}F NMR (DMSO-d_6) δ −153.20 (t, 1F, J=19.8 Hz), −160.44 (d, 1F, J=17.1 Hz), −163.42 (d, 1F, J=21.0 Hz); IR (Nujol) 3404, 3336, 3134, 1670, 1632 cm^{-1}. HRMS calcd for $C_{15}H_{12}F_3N_5O$: 335.0994. Found: 335.0990.

4.5.2. (*Z*)-*N*-[4,5,7-Trifluoro-6-(*N,N*-dimethylamino)-1*H*-indazol-3-yl]-*N′*-hydroxy-benzamidine 12b. Yield: 0.32 g, 93%, mp 196–198 °C (white crystals from H_2O/EtOH); ^{1}H NMR (DMSO-d_6) δ 2.93 (s, 6H), 7.29 (br s, 3H), 7.37 (br s, 2H), 8.33 (s, 1H, exch. D_2O), 10.53 (s, 1H, exch. D_2O), 13.00 (s, 1H, exch. D_2O); ^{19}F NMR (DMSO-d_6) δ −147.68 (d, 1F, J=20.1 Hz), −151.66 (t, 1F, J=20.4 Hz), −156.73 (d, 1F, J=21.3 Hz); IR (Nujol) 3400, 3275, 1657 cm^{-1}. HRMS calcd for $C_{16}H_{14}F_3N_5O$: 349.1150. Found: 349.1143.

4.5.3. (*Z*)-*N*-[4,5,7-Trifluoro-6-(*N*-methylamino)-1*H*-indazol-3-yl]-*N′*-hydroxy-acetamidine 12c. Yield: 0.27 g, 98%, mp 200–202 °C (white crystals from H_2O/EtOH); ^{1}H NMR (DMSO-d_6) δ 2.00 (s, 3H), 3.05 (t, 3H, J=4.27 Hz), 5.74 (s, 1H, exch. D_2O), 7.93 (s, 1H, exch. D_2O), 9.76 (s, 1H, exch. D_2O), 12.77 (s, 1H, exch. D_2O); ^{19}F NMR (DMSO-d_6) δ −155.13 (t, 1F, J=20.7 Hz), −160.21 (d, 1F, J=19.2 Hz), −162.94 (d, 1F, J=13.5 Hz); IR (Nujol) 3386, 3269, 1676, 1647 cm^{-1}. HRMS calcd for $C_{10}H_{10}F_3N_5O$: 273.0837. Found: 273.0838.

4.5.4. (*Z*)-*N*-[4,5,7-Trifluoro-6-(*N,N*-dimethylamino)-1*H*-indazol-3-yl)-*N′*-hydroxy-acetamidine 12d. Yield: 0.27 g, 96%, mp 203–206 °C (white crystals from H_2O/EtOH); ^{1}H NMR (DMSO-d_6) δ 1.98 (s, 3H), 2.97 (s, 6H), 8.04 (s, 1H, exch. D_2O), 9.79 (s, 1H, exch. D_2O), 13.17 (s, 1H, exch. D_2O); ^{19}F NMR (DMSO-d_6) δ −147.46 (d, 1F, J=20.1 Hz), −153.73 (t, 1F, J=20.7 Hz), −156.41 (br s, 1F); IR (Nujol) 3384, 3265, 1675, 1647 cm^{-1}. HRMS calcd for $C_{11}H_{12}F_3N_5O$: 287.0994. Found: 287.0988.

4.5.5. (*Z*)-*N*-(4,5,7-Trifluoro-6-methoxy-1*H*-indazol-3-yl)-*N′*-hydroxy-benzamidine 12e. Yield: 0.31 g, 93%, mp 185–188 °C (white crystals from H_2O/EtOH); ^{1}H NMR (DMSO-d_6) δ 4.07 (s, 3H), 7.25–7.30 (m, 3H), 7.33–7.40 (m, 2H), 8.39 (s, 1H, exch. D_2O), 10.56 (s, 1H, exch. D_2O), 13.21 (s, 1H, exch. D_2O); ^{19}F NMR (DMSO-d_6) δ −143.01 (t, 1F, J=21.0 Hz), −146.79 (d, 1F, J=20.7 Hz), −155.92 (d, 1F, J=21.9 Hz); IR (Nujol) 3385, 3142, 3057, 1670, 1639 cm^{-1}; HRMS calcd for $C_{15}H_{11}F_3N_4O_2$: 336.0834. Found: 336.0835.

4.5.6. (*Z*)-*N*-(4,5,7-Trifluoro-6-methoxy-1*H*-indazol-3-yl)-*N′*-hydroxy-acetamidine 12f. Yield: 0.25 g, 93%, mp 208–211 °C (white crystals from H_2O/EtOH); ^{1}H NMR (DMSO-d_6) δ 1.96 (s, 3H), 4.07 (s, 3H), 8.08 (s, 1H, exch. D_2O), 9.80 (s, 1H, exch. D_2O), 13.37 (s, 1H, exch. D_2O); ^{19}F NMR (DMSO-d_6) δ −144.96 (t, 1F, J=18.6 Hz), −146.52 (d, 1F, J=18.3 Hz), −155.60 (br s, 1F); IR (Nujol) 3389, 3252, 1657 cm^{-1}. HRMS calcd for $C_{10}H_9F_3N_4O_2$: 274.0678. Found: 274.0671.

4.6. Hydrolysis of (*Z*)-*N*-(4,5,7-trifluoro-1*H*-indazol-3-yl)-*N′*-hydroxy-amidines 12a–f. General procedure

To a mixture of **12** (1.0 mmol) in ethanol (10 mL), concd hydrochloric acid (0.5 mL) was added. The solution was refluxed for 24 h. After removal of the solvent, the residue was treated with water, neutralized by the addition of solid $NaHCO_3$ and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated. Crystallization of the residue from the appropriate solvent gave the corresponding 3-amino-4,5,7-trifluoro-1*H*-indazoles **13a–c**.

4.6.1. 3-Amino-4,5,7-trifluoro-6-(*N*-methylamino)-1*H*-indazole 13a. Yield: 0.15 g, 67% from **12a**; 0.16 g, 75% from **12c**, mp 178–80 °C (white crystals from H_2O/EtOH); ^{1}H NMR (DMSO-d_6) δ 3.01 (t, 3H, J_{H-F}=5 Hz), 5.22 (s, 2H, exch. D_2O), 5.53 (s, 1H, exch. D_2O), 11.74 (s, 1H, exch. D_2O); ^{19}F NMR (DMSO-d_6) δ −145.65 (t, 1F, J=18.9 Hz), −152.28 (d, 1F, J=19.2 Hz), −157.82 (d, 1F, J=20.7 Hz); MS *m/z* 216 (M^+, 100); IR (Nujol) 3471, 3404, 3389, 3333, 3152, 1680 cm^{-1}; Anal. Calcd for $C_8H_7F_3N_4$: C, 44.45; H, 3.26; N, 25.92. Found: C, 44.70; H, 3.20; N, 25.80.

4.6.2. 3-Amino-4,5,7-trifluoro-6-(*N,N*-dimethylamino)-1*H*-indazole 13b. Yield: 0.14 g, 65% from **12b**; 0.17 g, 78% from **12d**, mp 149–150 °C (white crystals from H_2O/EtOH); ^{1}H NMR (DMSO-d_6) δ 2.91 (s, 6H), 5.35 (s, 2H, exch. D_2O), 12.10 (s, 1H, exch. D_2O); ^{19}F NMR (DMSO-d_6) δ −140.11 (d, 1F, J=19.8 Hz), −144.61 (t, 1F, J=20.7 Hz), −151.40 (d, 1F, J=21.9 Hz); MS *m/z* 220 (M^+, 100); IR (Nujol) 3429, 3392, 3342, 3170, 3132, 1670 cm^{-1}; Anal. Calcd for $C_{10}H_9F_3N_4$: C, 46.96; H, 3.94; N, 24.34. Found: C, 47.10; H, 3.80; N, 24.50.

4.6.3. 3-Amino-4,5,7-trifluoro-6-methoxy-1*H*-indazole 13c. Yield: 0.20 g, 92% from **12e**; 0.21 g, 98% from **12f**, mp 209–212 °C (white crystals from H_2O/EtOH); ^{1}H NMR (DMSO-d_6) δ 4.05 (s, 3H), 5.42 (s, 2H, exch. D_2O), 12.31 (S, 1H, exch. D_2O); ^{19}F NMR (DMSO-d_6) δ −143.42 (t, 1F, J=19.2 Hz), −147.27 (d, 1F, J=18.3 Hz), −158.85 (d, 1F, J=21.6 Hz); MS *m/z* 217 (M^+, 100); IR (Nujol) 3429, 3392, 3338, 3136, 3082, 1672 cm^{-1}; Anal. Calcd for $C_8H_6F_3N_3O$: C, 44.25; H, 2.79; N, 19.35. Found: C, 44.30; H, 2.80; N, 19.50.

4.7. Synthesis of 3-amino-4,5,7-trifluoro-6-methoxy-1*H*-indazole 13c

Pentafluorobenzonitrile **14** (1.93 g, 10 mmol) was added to a solution of *t*-BuOK (1.23 g, 11 mmol) in methanol (20 mL). The solution was stirred at rt for 4 h and, after addition of hydrazine monohydrate (0.5 g, 20 mmol), refluxed for 12 h. The solvent was then evaporated under reduced pressure and the residue chromatographed to yield 3-amino-4,5,7-trifluoro-6-methoxy-1*H*-indazole **13c** (0.5 g, 23%).

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References and notes

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