DOI: 10.1002/ejoc.200901102

Trifluoro-3-hydroxy-1*H*-indazolecarboxylic Acids and Esters from Perfluorinated Benzenedicarboxylic Acids

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Dedicated to Professor Josep Font on the occasion of his 70th birthday

Keywords: Nitrogen heterocycles / Indazoles / Tautomerism / Fluorine

Twelve new 3-hydroxyindazoles, each bearing three fluorine substituents and a CO_2R group (R = H, CH_3, C_2H_5) distributed around its 4-, 5-, 6-, and 7-positions, have been synthesized. They were studied by NMR in solution (^1H, ^{13}C, ^{15}N, ^{19}F) and in the solid state (^{13}C, ^{15}N). In solution, all of them are 3-hydroxy tautomers: the **a** form. In the solid state, although the 3-hydroxy tautomers are still the most frequent, there are some cases of indazolin-3-ones – the **b** form – and one example (**12ab**) of the very rare case in which both tautomers are present.

Introduction

For a long time, indazoles were mainly considered a subset of pyrazoles (benzopyrazoles) but their individuality has been becoming more and more apparent (our interest in indazoles and their properties has been continuous over the years).[1] This is mainly due to the presence of indazole systems in many drugs and to the fact that their aza derivatives are related to purines. In the 2008 Chemical Abstracts, for instance, there are 250 references to indazoles, of which 55% are patents and 45% publications. The indazole moiety is a frequently found subunit in pharmaceuticals with important biological[2] and powerful pharmacological activities, including anti-inflammatory,[3] selective inhibition of factor Xa,[4] anti-tumor,[5,6] anti-HIV,[7] anti-platelet aggregation,[8] and antifungal activities,[9] plus serotonin 5-HT3 receptor antagonist activity.[10] A field in which indazoles are of particular relevance is as inhibitors of the different isoforms of nitric oxide synthase (NOS).[11] As a result of all these properties a variety of methods for the preparation of indazoles have been reported.[12,13]

Because some indazolin-3-ones (or 3-hydroxyindazoles) have shown high affinities for the NOS enzymes,[14] we decided to synthesize a series of trifluoro derivatives of 3-hydroxyindazoles (5,6,7; 4,6,7; 4,5,7; 4,5,6), each bearing on its remaining carbon atom (4; 5; 6; 7) a carboxy group either free or in its ester form (methyl or ethyl) to modify their physicochemical properties. The twelve compounds are represented in Scheme 1 (in the frame), together with 1*H*-indazol-3-ol (**13**) and 4,5,6,7-tetrafluoro-1*H*-indazol-3-ol (**14**).

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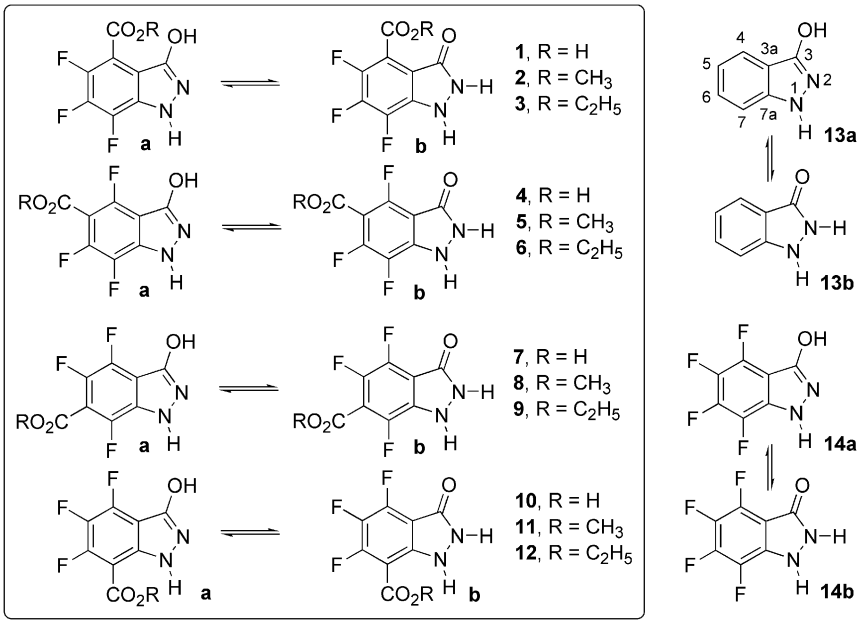
Results and Discussion

Synthesis

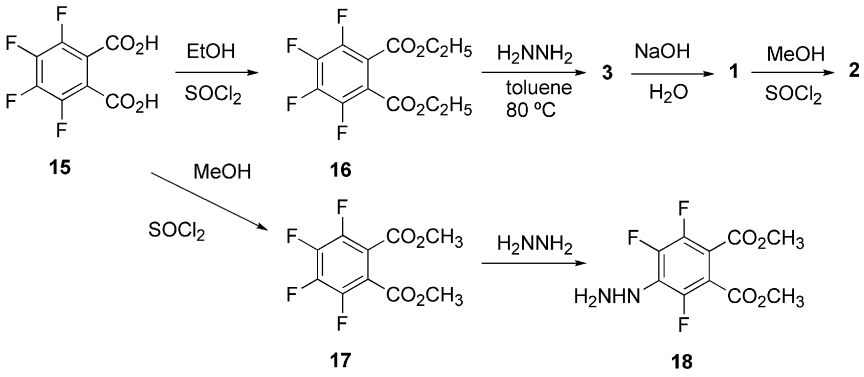
The title compounds were prepared by a method similar to that described for 4,5,6,7-tetrafluoro-3-methyl-1*H*-indazole[15] and 4,5,6,7-tetrafluoro-1*H*-indazol-3-ol (**14**).[1i] Scheme 2 depicts the synthetic pathways that yielded the 5,6,7-trifluoro-substituted derivatives **1**–**3**.

In general, reactions between hydrazine and tetrafluorophthalate esters can take place either in the *ortho* or in the *para* positions relative to the ester groups. In the first case this would lead to 5,6,7-trifluoro-3-hydroxy-1*H*-indazole-4-carboxylate esters (**2** and **3**) and in the second to hydrazine derivatives. The ethyl ester **16** afforded **3**, but the methyl ester **17** yielded **18**, isolated as dimethyl 3,4,6-trifluoro-5-[2-(propan-2-ylidene)hydrazinyl]phthalate {^1H NMR ($CDCl_3$, 400 MHz): δ = 6.92 (s, 1 H, N*H*), 3.89 and 3.87 (s, 6 H, –OCH_3), 2.03 and 1.91 [s, 6 H, (CH_3)$_2$C=N–] ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 15.1 and 24.7 ppm [(*C*H$_3$)$_2$-C=N–], 52.4 (–O*C*H$_3$), 52.6 (–O*C*H$_3$), 108.5 (C-2), 117.6 (C-1), 127.9 (C-5), 140.9 (C-3), 144.0 (C-6), 147.0 (C-4), 151.7 [(CH$_3$)$_2$*C*=N–], 162.5 (*C*O$_2$CH$_3$) and 163.2 (*C*O$_2$CH$_3$) ppm}, under any conditions attempted (toluene, THF, or DMF). The behavior of **17** is similar to that of tetrafluorophthalonitrile.[16]

Saponification of **3** gave 5,6,7-trifluoro-3-hydroxy-1*H*-indazole-4-carboxylic acid (**1**), which on esterification with methanol afforded **2**.

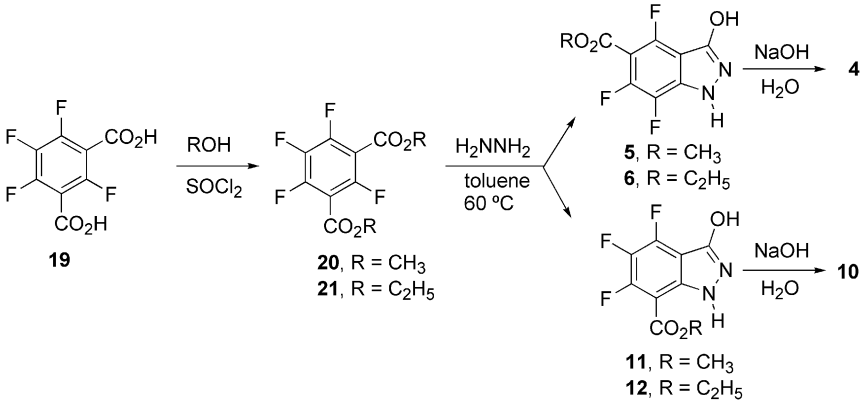


Scheme 1.



Scheme 2.

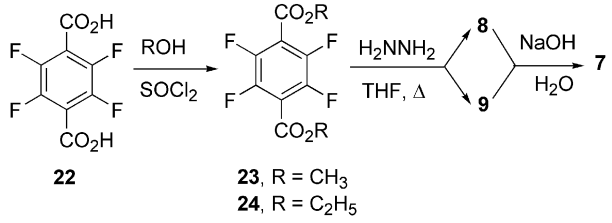
The esters **20** and **21** (Scheme 3) were prepared from 2,4,5,6-tetrafluoroisophthalic acid (**19**). Treatment of either **20** or **21** with hydrazine in toluene at 60 °C in each case afforded a mixture of isomers, with compounds **11** and **12**, each substituted with a CO_2R group at its 7-position, predominating. In each case the ratio of isomers determined from the ^1H NMR spectrum of the crude product was about 2 (7-CO_2R):1 (5-CO_2R).



Scheme 3.

If this reaction was carried out in THF with addition of hydrazine at room temperature, however, the 5-substituted derivatives **5** and **6** were the only compounds isolated, although in low yields. This is probably a consequence of steric hindrance around the 2-position; it seems that hydrazine is only able to overcome the energy barrier to reach carbon C-2 when added at 60 °C.

Finally, the syntheses of 4,5,7-trifluoro-3-hydroxy-1*H*-indazole-6-carboxylic acid (**7**) and its methyl and ethyl esters **8** and **9** are shown in Scheme 4.



Scheme 4.

As depicted in the above schemes, the trifluoro-3-hydroxy-1*H*-indazolecarboxylic acids **1**, **4**, **7**, and **10** were obtained in fair yields by hydrolysis of the corresponding esters under mild conditions. Save in the case of the last-mentioned derivative, by-products resulting from decarboxylation were identified by ^{1}H NMR in the reaction mixtures. The loss of CO_2 from perfluorinated aromatic acids has been reported and can, depending on the reaction conditions, predominate over nucleophilic substitution.[17]

NMR Studies

With the goal of achieving the complete characterization of all the preceding indazole derivatives **1**–**12** we performed an NMR study in solution ([D$_6$]DMSO, in some cases also including low-temperature experiments in [D$_8$]THF at 207 K). The data obtained are fully described in the Experimental.

In order to establish the main existing tautomeric form, however, we next discuss the most representative features with reference to the already published 4,5,6,7-tetrafluoro-1*H*-indazol-3-ol (**14**).[1i]

The chemical shifts of the NH and OH protons, the assignment of which was achieved by means of heteronuclear ^{1}H–^{15}N correlation experiments, clearly indicate that they are 3-hydroxy-1*H*-indazoles (**a**), with values close to those of **14a**: δ_{NH} = 12.7, δ_{OH} = 11.3 ([D$_6$]DMSO).[1i] The differences with regard to **14a** are found in the OH signals of **2** and **3** and in the NH signals of **11** and **12**, and are presumably due to intramolecular hydrogen bonds (IMHBs) with the ester group carbonyl moieties (Figure 1).

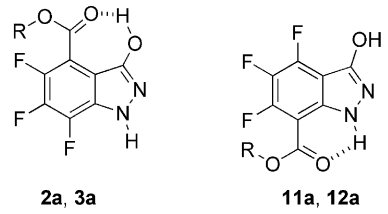


Figure 1. Intramolecular hydrogen bonds (IMHBs) present in 4-CO_2R and 7-CO_2R 1*H*-indazoles.

With regard to the ^{19}F NMR chemical shifts, the principal means to achieve reliable assignment was analysis of the multiplicities of the signals due to carbon–fluorine couplings, mainly the $^1J_{C,F}$ values of about 250 Hz. The $^3J_{F,F}$ and $^5J_{F,F}$ values lie within normal ranges, with average values of 20 Hz.[1i] Assignment of the ^{13}C NMR spectroscopic data proved to be straightforward considering the large number of ^{13}C chemical shifts reported for indazoles,[18] even though the spectra of these derivatives show complex multiplets owing to the aforementioned ^{13}C–^{19}F couplings.

As the outcome of the analysis of all the data set, we have summarized the shift effects for acids **1**, **4**, **7**, and **10** (those of the esters are very similar) in relation to **14**.[1i] The averaged values of the four situations are shown on the right-hand side of Figure 2. The effects on the ^{13}C chemical shifts are similar to those reported for monosubstituted benzenes (fluorobenzene vs. benzoic acid): *ipso* –32.2 ppm, *ortho* 15.6 ppm, and *para* 9.0 ppm.[19] The *ortho* and *para* ^{19}F chemical shifts and $^1J_{C,F}$ coupling constants are also very sensitive to the replacement of a F atom by a CO_2H group. The effects are relatively homogeneous, notwithstanding that the pyrazole nucleus alters the symmetry of the benzene ring.

This kind of analysis is of double interest: i) it serves to test the assignment of all signals, and ii) it establishes that the predominant tautomer is the same in all of compounds **1**–**12** and **14**. All are either 3-hydroxy-1*H*-indazoles (**a**) or mixtures very rich in this form (probably more than 95%).

^{15}N NMR spectroscopic data (Table 1, data for **2**, **5** and **8** have not been recorded), obtained by ^{1}H–^{15}N 2D inverse proton heteronuclear shift correlation experiments in [D$_8$]-THF at 207 K (no correlations were detected at room temperature), again indicate that these derivatives exist as 3-

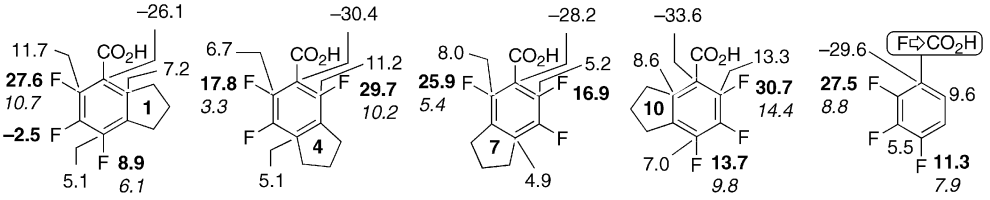


Figure 2. Effects on the ^{13}C chemical shifts (ppm, normal type), ^{19}F chemical shifts (ppm, bold type), and on $^1J_{C,F}$ (Hz, italics) produced by the replacement of a fluorine group in **14** by a carboxylic acid group as in acids **1**, **4**, **7** and **10**.

Table 1. Solution ^{15}N NMR chemical shifts (δ in ppm) and coupling constants (J in Hz).

	1	**3**	**4**	**6**	**7**	**9**	**10**	**11**	**12**	**14**[a]
N-1	[b]	–229.0 ^1J = 96.7	–228.1	–227.7	–230.1 ^1J = 92.3	–229.7 ^1J = 91.6	–221.6 ^1J = 114.7	–220.2	–220.1	–233.4
N-2	[b]	–104.6	–112.1	–111.4	–105.4	–104.8	–111.5	–109.7	–109.5	–111.9

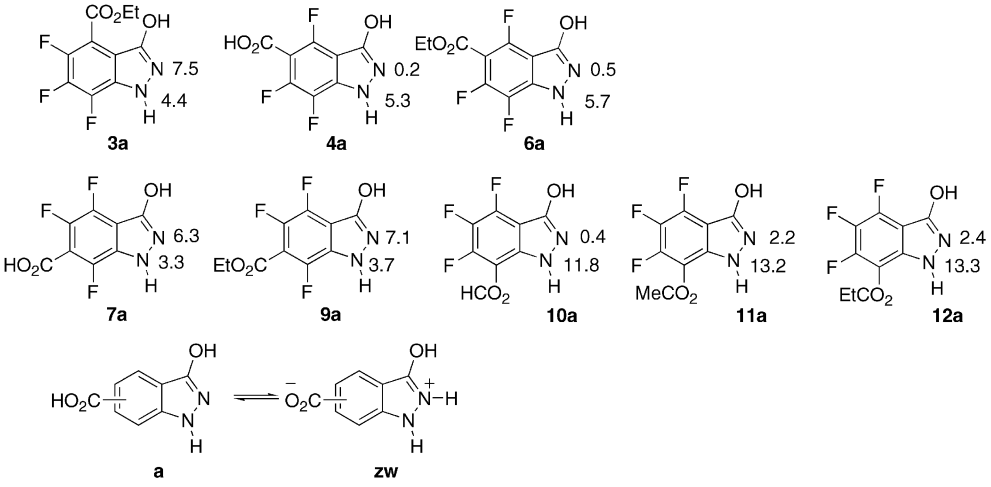
[a] From reference 1i. [b] Not observed either in [D_8]THF at 207 K or in [D_6]acetone at 185 K.

hydroxy-1*H*-indazoles.[1b,20,21] The abnormally high N-1 chemical shift value for 4,5,6-trifluoro-3-hydroxy-1*H*-indazole-7-carboxylic acid (**10**) and its two esters (**11** and **12**) is explained by the presence of the intramolecular hydrogen bond shown above in Figure 1.

The effects on the ^{15}N chemical shifts (ppm) due to the replacement of a fluorine in **14a** by a carboxylic group are summarized in Scheme 5. The presence of zwitterions (**zw**) in solution in the cases of acids **4a**, **7a**, and **10a** is excluded as the values are very similar to those of the corresponding esters **6a**, **9a**, **11a**, and **12a**, and besides, N-2 protonation of indazoles should cause shifts of δ = –125 ppm.[22]

In conclusion, the ^1H, ^{13}C, and ^{15}N NMR results demonstrate that compounds **1**–**12** exist in solution ([D_6]DMSO and [D_8]THF) as the 3-hydroxyindazole tautomers (**a**).

^{13}C and ^{15}N NMR chemical shifts in the solid state are shown in Table 2. In particular, the $\delta^{15}N$ values are considerably shifted relative to what is observed in solution



Scheme 5.

Table 2. ^{13}C and ^{15}N CPMAS NMR chemical shifts (δ in ppm) at 300 K.

	N-1	N-2	C-3	C-3a	C-4	C-5	C-6	C-7	C-7a	Other
1	–236.1 –227.7	–134.0	155.0	105.7	110.3	138[c]	138[c]	138[c]	126.5	CO_2H 170.2
2	–223.2	–117.2	156.1	106.1	106.1	148[c]	140[c]	140[c]	129.2	CH_3 54.5 CO 168.1
3	–223.4	–115.2	155.6	106.0	106.0	148[c]	141[c]	138[c]	128.0	CH_3 12.3, CH_2 64.6 CO 166.9
4	–256.6	–209.7	158.4	99.9	148[c]	104.1	148[c]	135.1	132.8	CO_2H 164.9
5	–228.8	–135.3	156.1	100.9	147[c]	100.9	147[c]	134[c]	133.7	CH_3 53.5 CO 163.7
6	–228.7	–131.7	156.0	99.0	149[c]	99.0	149[c]	132[c]	132.2	CH_3 11.8, CH_2 63.8 CO 161.8
7	–228.9	–121.7	154.6	102.4	139[c]	139[c]	109.7	139[c]	126.0	CO_2H 166.8
8	–230.0	–123.5	154.8	103.0	140[c]	140[c]	108.3	140[c]	125.8	CH_3 55.2 CO 163.0
9	–231.3	–123.0	155.1	104.0	143[c]	143[c]	106.5	143[c]	136.1	CH_3 13.6, CH_2 65.5 CO 162.1
10	–247.9	–209.4	157.0	96.8	150[c]	136[c]	150[c]	98.8	136.1	CO_2H 166.4
11	–226.4	–134.3	154.4	97.1	148[c]	133[c]	148[c]	97.1	136.6	CH_3 53.9 CO 164.9
12	–222.0[a] –242.7[b]	–123.9[a] –204.2[b]	154.4[a] 156.1[b]	95.6 97.0	147[c]	135[c]	150[c]	98.2 99.2	135.1 136.8	CH_3 12.8, 13.8 CH_2 62.2 CO 163.7

[a] Tautomer **a**. [b] Tautomer **b**. [c] Broad signal.

(Table 1). This must be due either to changes in the tautomer present in the solid state (large differences) or to intermolecular hydrogen bonding associations (small differences).

We will assume that the compounds studied in this work crystallize with formation of dimers (Figure 3) of two types: the indazolin-3-one[1b] type as in **13bb** or the 3-hydroxy-1*H*-indazole type as in **25aa**,[21] both structures being connected by double proton transfer.

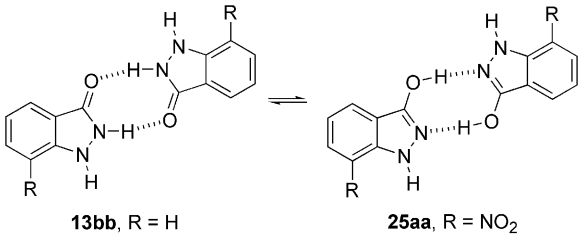


Figure 3. Dimers formed by NH···O and OH···N intermolecular hydrogen bonds.

From the most representative NMR criteria for tautomeric assignment – hydroxy (**a**), δN-1 (–222/–236 ppm), δN-2 (–117/–135 ppm), δC-3 (153/156 ppm); oxo (**b**), δN-1 (–243/–257 ppm), δN-2 (–204/–210 ppm), δC-3 (156/158 ppm) – we have established that in solution all derivatives **1**–**12** exist as their 3-hydroxy-1*H*-indazole tautomers (**a**). In the solid state, seven out of the eight esters maintain the same tautomer (**a**). The only exception is ethyl 4,5,6-trifluoro-3-hydroxy-1*H*-indazole-7-carboxylate (**12**), which exists as a mixture of tautomers (Figure 4a and 4b), the assignment of which is given in Figure 5.

A comparative analysis of chemical shifts encountered for the 3-hydroxy-1*H* tautomers in solution and in the solid state for compounds **11**, **12**, and 7-nitro-1*H*-indazol-3-ol (**25**)[21] is shown in Table 3, and led us to propose for **11** a crystalline structure (**11aa**, Figure 6) fairly similar to that of **25aa** (Figure 4).

The δN-1 value for the 1*H*-3-hydroxy tautomer of **12** in solution is practically the same as in the solid state; the environment of N-1 scarcely varies as a result of the IMHBs between the ethoxycarbonyl and the NH groups (Figure 1). On the other hand, the signal for N-2 is shifted by almost 15 ppm due to the formation in the solid state of one hydrogen bond that does not exist in solution ([D_8]THF). With all these data taken into account, a plausible solid-state structure for **12** could be the mixed dimer shown in Figure 6 (**12ab**). The slight difference (of 1.7 ppm) between the tautomers of **12** seen in the case of δC-3, in comparison with that of 8.4 ppm observed for **14**, also supports the hypothesis. The presence of two tautomers with a 1:1 stoichiometry in a crystalline solid is a rare phenomenon; the closest example is 3-methyl-1-phenylpyrazolin-5-one, which crystallizes in chains (catemer) formed by oxo and hydroxy tautomers.[23,24]

A comparative analysis of chemical shifts similar to that already discussed (Table 3) for other indazoles is presented in Table 4.

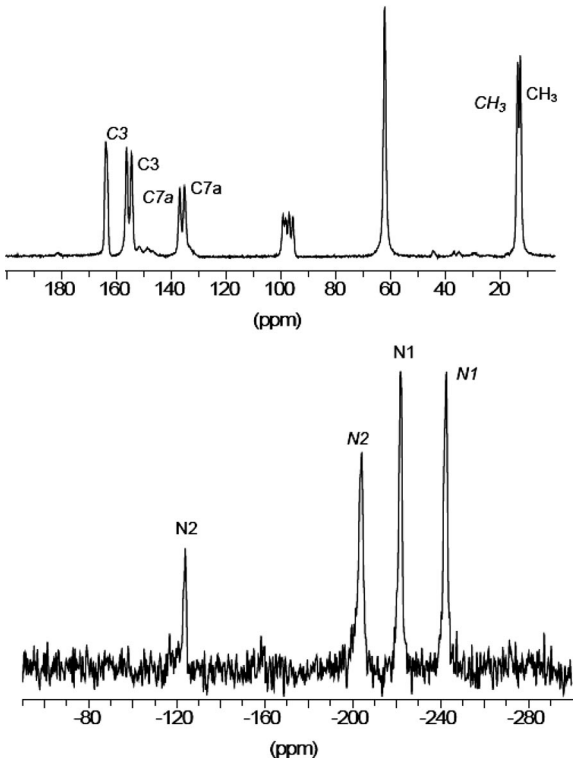


Figure 4. Top) ^{13}C NMR CPMAS spectrum of compound **12**; **12a** in normal type and **12b** in italics. Bottom) ^{15}N NMR CPMAS spectrum of compound **12**; **12a** in normal type and **12b** in italics.

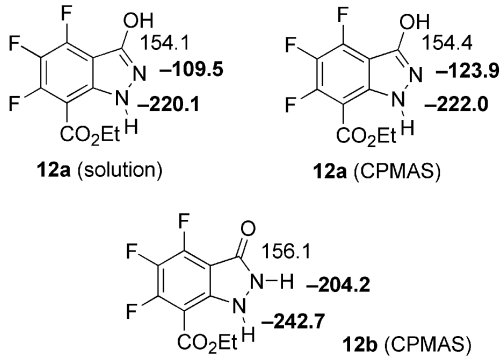


Figure 5. N-1, N-2 (bold type), and C-3 (normal type) chemical shifts of **12** in solution and in the solid state.

Table 3. Differences (ppm) and ratios between solution and solid-state chemical shifts.

		11aa	**12ab**	**25aa** dimer
N-1	difference	6.2	1.9	6.4
	ratio	0.973	0.991	0.972
N-2	difference	24.6	14.4	25.9
	ratio	0.817	0.884	0.813

The two ethyl esters **6** and **9** and the carboxylic acid **7** show the same trend: a slight variation in N-1 and a remarkable increase in N-2. In addition to their existing as their 3-hydroxy tautomers, the small chemical shift differences between these two compound frameworks and their methyl analogues **5** and **8** suggest that these four derivatives

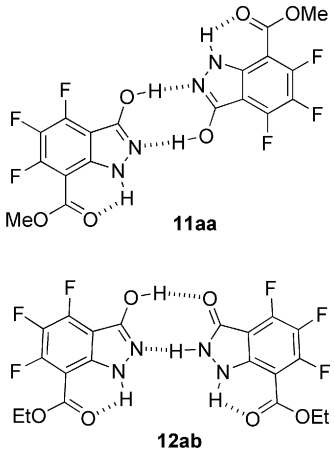


Figure 6. Dimers formed by OH···N, OH···O and NH···N intermolecular hydrogen bonds.

Table 4. Differences (ppm) between the solution and solid-state chemical shifts, together with ratios.

		3	4	6	7	9	10
N-1	difference	–5.6	–28.5	1.0	–1.2	1.6	–26.3
	ratio	1.025	0.889	0.996	1.005	0.993	0.893
N-2	difference	10.6	–97.6	20.3	16.3	18.2	–97.9
	ratio	0.908	0.535	0.846	0.866	0.852	0.532

should be arranged in similar modes in their crystalline structures, probably involving N–H···N hydrogen bonds, although involvement of the carbonyl oxygen in the alkoxycarbonyl group in hydrogen bonding cannot be ruled out.[25,26] With regard to compound **3**, the values reported in Table 4 are significantly different; probably an IMHB between ethoxycarbonyl and OH groups prevents the formation of dimeric structures such as those shown in Figures 3 and 6. The expected molecular association for **3** should be one of those typical for 1*H*-indazoles (NH···N dimers, trimers, or catemers).[27] Compound **2** shows practically the same ^{15}N CPMAS chemical shift values as **3** (Table 2) and so the same solid-state structure is expected for both (Figure 7).

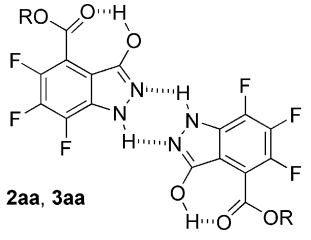


Figure 7. Dimers formed by intermolecular N–H···N hydrogen bonds.

Finally, compounds **4** and **10** exist in the solid state as indazolin-3-ones (**b**), as can be deduced from Figure 8, in which the structures of both tautomers and their corresponding δN-1, δN-2 and δC-3 values are reported.

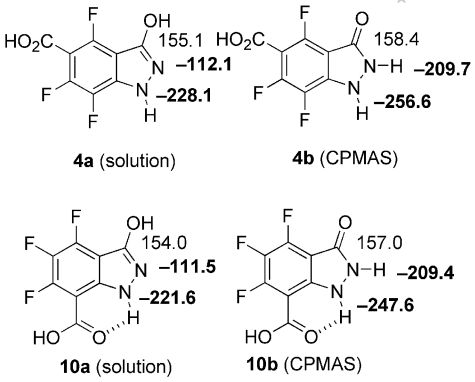


Figure 8. Values for δN-1, δN-2, and δC-3 of compounds **4** and **10** in solution and in the solid state.

Conclusions

Twelve trifluoro-3-hydroxyindazole carboxylic acids and esters (Scheme 1) have been prepared in fair yields from starting commercially available perfluorobenzenedicarboxylic acids (3,4,5,6-tetrafluorophthalic acid, 2,4,5,6-tetrafluoroisophthalic acid, and 2,3,5,6-tetrafluoroterephthalic acid). A discussion of the synthetic procedures – the influence of the experimental conditions, the formation of isomers, as well as the decarboxylation by-products – is presented.

In general, of the four possible tautomeric forms of 3-hydroxyindazoles, only tautomers **a** (3-hydroxy-1*H*-indazole) and **b** (indazolin-3-one) have been observed (Figure 9). Tautomer **c** is a 2*H*-3-hydroxyindazole and, like all NH-indazoles, is much less stable than the 1*H* tautomers.[1b,28,29,30] The non-aromatic character of tautomer **d** explains its non-existence. In the solid state (X-ray determination), indazolinone itself [R = H (**13**)] exists as such (**13b**).[1b] A search in the Cambridge Structural Database (CSD)[31] shows that only for this compound (refcode FADMIG) has an indazolinone structure been reported. A recent publication based on X-ray crystallography as well as ^{13}C and ^{15}N CPMAS NMR describes a new polymorph of **13**, but it is still tautomer **13b**, whereas the 7-nitro derivative **25** crystallizes as the 3-hydroxy tautomer **25a** (Figure 3).[21]

In this work, 3-hydroxyindazoles present a case of tautomerism in which the hydroxy (**a**) and oxo (**b**) tautomers both have similar stabilities. The predominance of one form or the other is modulated by the natures of the substituents on the benzene ring and by the phase. In solution, every combination of three fluorine atoms and one CO_2R group leads to the predominance of the OH tautomer (**a**), independently of the presence or absence of IMHBs. In the solid state, the situation is more balanced: although **a** still predominates (9.5 out of 12 cases), the oxo tautomer is present in 2.5 cases (the 5-carboxylic acid **4b**, the 7-carboxylic acid **10b**, and half the molecules of the 7-ethoxycarbonyl ester **12ab**). In the absence of X-ray data, SSNMR proves to be a powerful tool for establishing the molecular structures of

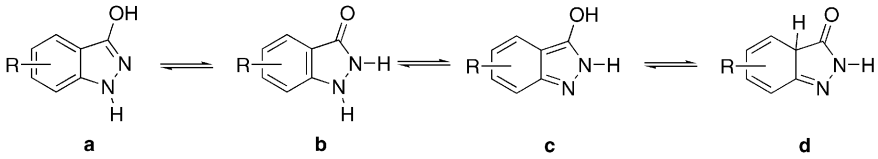


Figure 9. The four possible tautomers of 3-hydroxyindazoles.

these heterocyclic compounds of major importance in order to understand their biological and pharmaceutical activities.

Experimental Section

General: All chemicals were used as provided without further purification. Melting points were determined by microscopy (Thermo-Galen hot stage) or by DSC (Seiko 220C) with a scanning rate of 5.0 °C min^{-1}. Thin-layer chromatography (TLC) was performed with Merck silica gel (60 F254). Compounds were detected with the aid of a 254 nm UV lamp. Silica gel (70–320 mesh) was employed for routine column chromatography separations with the indicated eluents. Microanalyses were determined at the "Centro de Análisis Elemental-UCM, Madrid" [Perkin–Elmer 240 (CHN)].

Solution spectra were recorded with a Bruker DRX 400 spectrometer (9.4 T, 400.13 MHz for ^{1}H, 100.62 MHz for ^{13}C, 376.50 MHz for ^{19}F, and 40.56 MHz for ^{15}N). Chemical shifts (δ in ppm) are given from internal solvent for ^{1}H and ^{13}C and from an external reference ($CFCl_3$) for ^{19}F, whereas for ^{15}N NMR nitromethane (0.00) was used as external standard. Variable-temperature experiments were recorded with the same spectrometer. A Bruker BVT3000 temperature unit was used to control the temperature of the cooling gas stream and an exchanger to achieve low temperatures.

Solid-state ^{13}C (100.73 MHz) and ^{15}N (40.60 MHz) CPMAS NMR spectra were obtained with a Bruker WB 400 spectrometer at 300 K with use of a 4 mm DVT probehead. ^{13}C spectra were originally referenced to a glycine sample and the chemical shifts were then recalculated to the Me_4Si [for the carbonyl atom $\delta_{(glycine)}$ = 176.1 ppm] and ^{15}N spectra to $^{15}NH_4Cl$ and then converted to the nitromethane scale with the aid of the relationship: $\delta^{15}N(MeNO_2) = \delta^{15}N(NH_4Cl) - 338.1$ ppm.

General Procedure for Esterifications: A solution of a diacid (**15**, **19**, **22**, 4.2 mmol, 1.0 g) in dry ethanol/methanol (10 mL) was prepared in a three-necked, round-bottomed flask fitted with a reflux condenser and a calcium chloride tube. The flask was placed in an ice/water bath, thionyl chloride (1.4 mL) was then added dropwise, and the mixture was heated at 60–65 °C for four days. After removal of solvent, the resulting residue was purified by column chromatography (hexane/diethyl ether 8:1).

Diethyl 3,4,5,6-Tetrafluorophthalate (16): White solid, yield 87%, m.p. 30 °C (lit[32] 29 °C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.39 (t, ^3J = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 4.42 (q, ^3J = 7.1 Hz, 2 H, $CO_2CH_2CH_3$) ppm.

Dimethyl 3,4,5,6-Tetrafluorophthalate (17): White solid, yield 75%, m.p. 72 °C (lit[33] 70–73 °C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.95 (s, 3 H, CO_2CH_3) ppm.

Dimethyl 2,4,5,6-Tetrafluoroisophthalate (20): Yellowish oil, yield 84% (lit[34] m.p. 36–37.5 °C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.87 (s, 3 H, CO_2CH_3) ppm.

Diethyl 2,4,5,6-Tetrafluoroisophthalate (21): Colorless oil, yield 85% (lit[35] b.p. 126–129 °C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.31 (t, ^3J = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 4.35 (q, ^3J = 7.1 Hz, 2 H, $CO_2CH_2CH_3$) ppm.

Dimethyl 2,3,5,6-Tetrafluoroterephthalate (23): White solid, yield 98%, m.p. 80 °C (lit[36] 79–80 °C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.00 (s, 3 H, CO_2CH_3) ppm.

Diethyl 2,3,5,6-Tetrafluoroterephthalate (24): Colorless oil, yield 90% (lit[37] b.p. 155–158 °C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.36 (t, ^3J = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 4.42 (q, ^3J = 7.1 Hz, 2 H, $CO_2CH_2CH_3$) ppm.

5,6,7-Trifluoro-3-hydroxy-1*H*-indazole-4-carboxylic Acid (1): Ethyl 5,6,7-trifluoro-3-hydroxy-1*H*-indazole-4-carboxylate (**3**, 0.6 mmol, 150 mg) and sodium hydroxide (2 mmol, 80 mg) were dissolved in water (5 mL) in a round-bottomed flask. The mixture was stirred at room temperature for 24 h. Concentrated hydrochloric acid was then added to reach pH 1 and the solution was cooled to 4 °C for a further 24 h. After filtration, the mother liquor was extracted with ethyl acetate (3 × 20 mL). The extracts were combined and dried with anhydrous magnesium sulfate, and after evaporation of solvent the residue was combined with the precipitate. The resulting solid was purified by column chromatography (hexane/diethyl ether 2:1). The product (100 mg) was obtained as a white solid (yield 72%); m.p. >300 °C (microscope). ^{1}H NMR ([D$_6$]DMSO, 400 MHz): δ = 12.6 (br. s, 1 H, N*H*), 11.4 (br. s, 1 H, O*H*) ppm. ^{13}C NMR ([D$_6$]DMSO, 100 MHz): δ = 156.6 (dd, ^4J = 5.2, ^4J = 2.7 Hz, C-3), 106.0 (dd, ^3J = 5.7, ^3J = 3.2 Hz, C-3a), 112.5 (m, C-4), 144.4 (dd, ^1J = 250.2, ^2J = 13.3 Hz, C-5), 138.6 (ddd, ^1J = 245.9, ^2J = 20.4, ^2J = 11.7 Hz, C-6), 136.6 (ddd, ^1J = 254.3, ^2J = 13.2, ^3J = 3.2 Hz, C-7), 127.3 (dd, ^2J = 12.6, ^3J = 2.5 Hz, C-7a), 165.0 (s, *C*O$_2$H) ppm. ^{19}F NMR ([D$_6$]DMSO, 376 MHz): δ = –143.1 (d, $^3J_{F\text{-}6}$ = 20.0 Hz, 1 F, F-5), –161.6 (dd, $^3J_{F\text{-}5}$ = 20.0, $^3J_{F\text{-}7}$ = 20.0 Hz, 1 F, F-6), –151.6 (d, $^3J_{F\text{-}6}$ = 20.0 Hz, 1 F, F-7) ppm. $C_8H_3F_3N_2O_3\cdot H_2O$ (250.13): calcd. C 38.41, H 2.01, N 11.20; found C 38.21, H 1.75, N 10.83.

Methyl 5,6,7-Trifluoro-3-hydroxy-1*H*-indazole-4-carboxylate (2): A solution of 5,6,7-trifluoro-3-hydroxy-1*H*-indazole-4-carboxylic acid (**1**, 0.26 mmol, 60 mg) in dry methanol (2 mL) was prepared in a three-necked, round-bottomed flask. The flask was placed on a water/ice bath and thionyl chloride (0.5 mL) was added dropwise under argon. The mixture was heated at 50 °C for 48 h. The solution was then allowed to cool to room temperature and the solvent was removed. Water (1 mL) was added to the residue and the resulting suspension was kept at 4 °C for 2 h. After filtration, the solid was washed with water and diethyl ether and dried in vacuo to provide pure product (40 mg, yield 63%); m.p. 215–217 °C (microscope). ^{1}H NMR ([D$_6$]DMSO, 400 MHz): δ = 12.8 (br. s, 1 H, N*H*), 10.9 (br. s, 1 H, O*H*), 3.91 (s, 3 H, CO_2CH_3) ppm. ^{13}C NMR ([D$_6$]DMSO, 100 MHz): δ = 155.3 (dd, ^4J = 5.2, ^4J = 2.7 Hz, C-3), 104.5 (dd, ^3J = 4.8, ^3J = 2.5 Hz, C-3a), 108.1 (dd, ^2J = 13.9, ^3J = 4.7 Hz C-4), 143.4 (dd, ^1J = 248.2, ^2J = 14.2 Hz, C-5), 138.1 (ddd, ^1J = 247.5, ^2J = 19.4, ^2J = 12.4 Hz, C-6), 137.0 (ddd, ^1J = 256.4, ^2J = 13.0, ^3J = 4.1 Hz, C-7), 127.5 (d, ^2J = 11.3 Hz, C-7a),

53.1 (s, CO_2CH_3), 163.0 (s, CO_2CH_3) ppm. ^{19}F NMR ([D$_6$]DMSO, 376 MHz): δ = –144.4 (d, $^3J_{F\text{-}6}$ = 18.4 Hz, 1 F, F-5), –161.2 (dd, $^3J_{F\text{-}5}$ = 18.4, $^3J_{F\text{-}7}$ = 18.4 Hz, 1 F, F-6), –150.0 (d, $^3J_{F\text{-}6}$ = 18.4 Hz, 1 F, F-7) ppm. $C_9H_5F_3N_2O_3$ (246.14): calcd. C 43.92, H 2.05, N 11.38; found C 43.83, H 2.18, N 11.10.

Ethyl 5,6,7-Trifluoro-3-hydroxy-1*H*-indazole-4-carboxylate (3): Hydrazine monohydrate (98%, 8.0 mmol, 400 mg) was added dropwise to a solution of diethyl 3,4,5,6-tetrafluorophthalate (**16**, 3.4 mmol, 1.0 g) in toluene (50 mL) in a three-necked, round-bottomed flask. The mixture was heated at 80 °C for five days and the toluene was then removed. The components of the resulting residue were separated by column chromatography (hexane/diethyl ether 8:1 to 1:1) to give both recovered starting material and the pure product (150 mg, yield 17%); m.p. 200–202 °C (microscope). ^1H NMR ([D$_6$]DMSO, 400 MHz): δ = 12.8 (br. s, 1 H, N*H*), 11.0 (br. s, 1 H, O*H*), 1.31 (t, ^3J = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 4.38 (q, ^3J = 7.1 Hz, 2 H,$CO_2CH_2CH_3$) ppm. ^{13}C NMR ([D$_6$]DMSO, 100 MHz): δ = 155.4 (dd, ^4J = 4.5, ^4J = 2.2 Hz, C-3), 104.5 (dd, ^3J = ^3J = 5.3 Hz, C-3a), 108.5 (dd, ^2J = 14.0, ^3J = 5.0 Hz C-4), 143.3 (dd, ^1J = 247.5, ^2J = 14.7 Hz, C-5), 138.1 (ddd, ^1J = 247.3, ^2J = 19.1, ^2J = 12.3 Hz, C-6), 136.9 (ddd, ^1J = 254.9, ^2J = 13.2, ^3J = 3.9 Hz, C-7), 127.5 (d, ^2J = 12.2 Hz, C-7a), 13.9 (s, $CO_2CH_2CH_3$) 62.2 (s, $CO_2CH_2CH_3$), 162.4 (s, $CO_2CH_2CH_3$) ppm. ^{19}F NMR ([D$_6$]DMSO, 376 MHz): δ = –144.9 (d, $^3J_{F\text{-}6}$ = 19.9 Hz, 1 F, F-5), –161.3 (dd, $^3J_{F\text{-}5}$ = 19.9, $^3J_{F\text{-}7}$ = 19.9 Hz, 1 F, F-6), –150.3 (d, $^3J_{F\text{-}6}$ = 19.9 Hz, 1 F, F-7) ppm. $C_{10}H_7F_3N_2O_3$ (260.17): calcd. C 46.16, H 2.71, N 10.77; found C 45.98, H 2.66, N 10.65.

4,6,7-Trifluoro-3-hydroxy-1*H*-indazole-5-carboxylic Acid (4): Methyl 4,6,7-trifluoro-3-hydroxy-1*H*-indazole-5-carboxylate (**5**, 0.53 mmol, 130 mg) and sodium hydroxide (1.8 mmol, 70 mg) were dissolved in water (5 mL) in a round-bottomed flask. The mixture was stirred at room temperature for 24 h. Concentrated hydrochloric acid was then added to reach pH 1 and the solution was cooled to 4 °C for a further 24 h. After filtration, the precipitate is purified by column chromatography (hexane/diethyl ether 3:1) to provide the pure product as a white solid (110 mg, yield 89%); m.p. >300 °C (microscope). A similar procedure was used to obtain **4** from **6**. ^1H NMR ([D$_6$]DMSO, 400 MHz): δ = 12.30 (s, 1 H, N*H*), 11.0 (br. s, 1 H, O*H*) ppm. ^{13}C NMR ([D$_6$]DMSO, 100 MHz): δ = 155.1 (s, C-3), 100.7 (dd, ^2J = 22.1, ^3J = 4.3 Hz, C-3a), 149.8 (dd, ^1J = 260.8, ^3J = 6.4 Hz, C-4), 102.3 (dd, ^2J = ^2J = 17.4 Hz, C-5), 145.6 (ddd, ^1J = 250.0, ^2J = 11.8, ^3J = 6.3 Hz, C-6), 132.1 (ddd, ^1J = 244.5, ^2J = 16.9, ^4J = 4.5 Hz, C-7), 132.7 (m, C-7a), 161.9 (s, CO_2H) ppm. ^{19}F NMR ([D$_6$]DMSO, 376 MHz): δ = –119.1 (d, $^5J_{F\text{-}7}$ = 19.5 Hz, 1 F, F-4), –141.3 (d, $^3J_{F\text{-}7}$ = 19.5 Hz, 1 F, F-6), –163.4 (dd, $^3J_{F\text{-}6}$ = 19.5, $^5J_{F\text{-}4}$ = 19.5 Hz,1 F, F-7) ppm. $C_8H_3F_3N_2O_3\cdot 0.5H_2O$ (241.12): calcd. C 39.85, H 1.67, N 11.62; found C 39.84, H 1.81, N 11.30.

Methyl 4,6,7-Trifluoro-3-hydroxy-1*H*-indazole-5-carboxylate (5): A solution of dimethyl 2,4,5,6-tetrafluoroisophthalate (**20**, 2.7 mmol, 800 mg) in tetrahydrofuran (40 mL) was prepared in a three-necked round-bottomed flask, and hydrazine monohydrate (98%, 6.0 mmol, 300 mg) was added dropwise. The solution was heated at 50 °C for 3 h and, after cooling to room temperature, the precipitate was filtered off and discarded. Column chromatography of the residue obtained after removal of THF (hexane/diethyl ether 4:1 to 1:1) afforded the pure product (120 mg, yield 16%); m.p. 273.8 °C (DSC). ^1H NMR ([D$_6$]DMSO, 400 MHz): δ = 13.0 (br. s, 1 H, N*H*), 11.4 (br. s, 1 H, O*H*), 3.86 (s, CO_2CH_3) ppm. ^{13}C NMR ([D$_6$]-DMSO, 100 MHz): δ = 155.2 (s, C-3), 100.6 (dd, ^2J = 22.6, ^3J = 5.0 Hz, C-3a), 150.3 (dd, ^1J = 263.1, ^3J = 6.9 Hz, C-4), 100.4 (dd, ^2J = ^2J = 15.1 Hz, C-5), 145.6 (ddd, ^1J = 251.2, ^2J = 12.6, ^3J = 6.3 Hz, C-6), 132.3 (ddd, ^1J = 244.9, ^2J = 16.3, ^4J = 5.0 Hz, C-7), 133.0 (m, C-7a), 52.7 (s, CO_2CH_3), 161.0 (s, CO_2CH_3) ppm. ^{19}F NMR ([D$_6$]DMSO, 376 MHz): δ = –117.7 (d, $^5J_{F\text{-}7}$ = 19.6 Hz, 1 F, F-4), –141.1 (br. s, F-6), –162.8 (dd, $^3J_{F\text{-}6}$ = 19.6, $^5J_{F\text{-}4}$ = 19.6 Hz,1 F, F-7) ppm. $C_9H_5F_3N_2O_3$ (246.14): calcd. C 43.92, H 2.05, N 11.38; found C 44.15, H 2.24, N 11.21.

Ethyl 4,6,7-Trifluoro-3-hydroxy-1*H*-indazole-5-carboxylate (6): Diethyl 2,4,5,6-tetrafluoroisophthalate (**21**, 1.7 mmol, 510 mg) was dissolved in tetrahydrofuran (25 mL) in a three-necked, round-bottomed flask. Hydrazine monohydrate (98%, 4.7 mmol, 235 mg) was then added dropwise, and the resulting mixture was heated at 80 °C for 15 h. The solution is decanted while hot and the solvent was removed under reduced pressure. The components of the residue were separated by column chromatography (hexane/diethyl ether 4:1 to 1:1) to afford the pure product (90 mg, yield 20%); m.p. 259.6 °C (DSC). ^1H NMR ([D$_6$]DMSO, 400 MHz): δ = 12.9 (br. s, 1 H, N*H*), 11.5 (br. s, 1 H, O*H*), 1.29 (t, ^3J = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 4.33 (q, ^3J = 7.1 Hz, 2 H,$CO_2CH_2CH_3$) ppm. ^{13}C NMR ([D$_6$]DMSO, 100 MHz): δ = 155.2 (s, C-3), 100.7 (dd, ^2J = 21.6, ^3J = 4.5 Hz, C-3a), 150.2 (dd, ^1J = 262.5, ^3J = 6.3 Hz, C-4), 100.9 (dd, ^2J = ^2J = 16.9 Hz, C-5), 145.5 (ddd, ^1J = 250.6, ^2J = 12.0, ^3J = 5.7 Hz, C-6), 132.1 (ddd, ^1J = 244.9, ^2J = 17.0, ^4J = 4.4 Hz, C-7), 132.9 (m, C-7a), 14.0 (s, $CO_2CH_2CH_3$) 61.6 (s, $CO_2CH_2CH_3$), 160.5 (s, $CO_2CH_2CH_3$) ppm. ^{19}F NMR ([D$_6$]-DMSO, 376 MHz): δ = –118.2 (d, $^5J_{F\text{-}7}$ = 19.6 Hz, 1 F, F-4), –141.3 (br. s, F-6), –162.8 (dd, $^3J_{F\text{-}6}$ = 19.6, $^5J_{F\text{-}4}$ = 19.6 Hz, 1 F, F-7) ppm. $C_{10}H_7F_3N_2O_3$ (260.17): calcd. C 46.16, H 2.71, N 10.77; found C 46.12, H 2.77, N 10.55.

4,5,7-Trifluoro-3-hydroxy-1*H*-indazole-6-carboxylic Acid (7): A solution of methyl 4,5,7-trifluoro-3-hydroxy-1*H*-indazole-6-carboxylate (**8**, 0.60 mmol, 0.14 g) and sodium hydroxide (1.3 mmol, 0.05 g) in water (5 mL) was stirred at room temperature for 24 h. Concentrated hydrochloric acid was then added to reach pH 1 and the solution was cooled to 4 °C for a further 24 h. After filtration of the precipitate, the pure product (110 mg , yield 79%) was collected; m.p. >300 °C (microscope). A similar procedure was used to obtain **7** from **9**. ^1H NMR ([D$_6$]DMSO, 400 MHz): δ = 12.25 (s, 1 H, N*H*), 10.7 (br. s, 1 H, O*H*) ppm. ^{13}C NMR ([D$_6$]DMSO, 100 MHz): δ = 154.4 (s, C-3), 103.7 (dd, ^2J = 18.3, ^3J = 4.4 Hz, C-3a), 138.3 (ddd, ^1J = 249.4, ^2J = 14.8, ^4J = 4.4 Hz, C-4), 137.9 (ddd, ^1J = 241.0, ^2J = 14.0, ^3J = 4.6 Hz, C-5), 110.7 (dd, ^2J = ^2J = 19.5 Hz, C-6), 139.8 (ddd, ^1J = 253.6, ^3J = 6.3, ^4J = 3.8 Hz, C-7), 128.6 (dd, ^2J = 18.3, ^3J = 6.9 Hz, C-7a), 161.7 (s, CO_2H) ppm. ^{19}F NMR ([D$_6$]DMSO, 376 MHz): δ = –151.0 (dd, $^3J_{F\text{-}5}$ = 21.4, $^5J_{F\text{-}7}$ = 21.4 Hz, 1 F, F-4), –153.8 (dd, $^3J_{F\text{-}4}$ = 21.4, $^4J_{F\text{-}7}$ = 3.7 Hz, 1 F, F-5), –134.6 (dd, $^5J_{F\text{-}4}$ = 21.4, $^4J_{F\text{-}5}$ = 3.7 Hz, 1 F, F-7) ppm. $C_8H_3F_3N_2O_3\cdot H_2O$ (250.13): calcd. C 38.41, H 2.01, N 11.20; found C 38.17, H 2.08, N 10.62.

Methyl 4,5,7-Trifluoro-3-hydroxy-1*H*-indazole-6-carboxylate (8): A solution of dimethyl 2,3,5,6-tetrafluoroterephthalate (**23**, 2.4 mmol, 1.1 g) in tetrahydrofuran (60 mL) was prepared in a three-necked, round-bottomed flask, and hydrazine monohydrate (98%, 8.0 mmol, 400 mg) was added dropwise. The mixture was heated at 60 °C for 6 h. After the solution had been allowed to cool to room temperature, the precipitate was filtered off and discarded. The residue obtained as a result of removal of THF was chromatographed (hexane/diethyl ether 4:1 to 1:1) to afford the pure product (500 mg, yield 45%); m.p. 243.9 °C (DSC). ^1H NMR ([D$_6$]DMSO, 400 MHz): δ = 12.9 (br. s, 1 H, N*H*), 11.4 (br. s, 1 H, O*H*), 3.92 (s, 3 H, CO_2CH_3) ppm. ^{13}C NMR ([D$_6$]DMSO, 100 MHz): δ = 154.5 (m, C-3), 104.3 (dd, ^2J = 20.0, ^3J = 5.7 Hz, C-3a), 138.5 (ddd, ^1J = 249.9, ^2J = 14.8, ^4J = 3.9 Hz, C-4), 138.0 (ddd, ^1J = 242.5, ^2J =

14.0, ^3J = 3.8 Hz, C-5), 108.8 (dd, ^2J = 18.8, ^2J = 15.0 Hz, C-6), 140.5 (ddd, ^1J = 251.7, ^3J = 5.2, ^4J = 2.5 Hz, C-7), 128.5 (dd, ^2J = 18.4, ^3J = 6.9 Hz, C-7a), 53.3 (s, CO_2CH_3), 160.9 (s, CO_2CH_3) ppm. ^{19}F NMR ([D$_6$]DMSO, 376 MHz): δ = –150.6 (dd, $^3J_{F-5}$ = 20.1, $^5J_{F-7}$ = 20.1 Hz, 1 F, F-4), –153.6 (dd, $^3J_{F-4}$ = 20.1, $^4J_{F-7}$ = 3.4 Hz, 1 F, F-5), –133.3 (dd, $^5J_{F-4}$ = 20.1, $^4J_{F-5}$ = 3.4 Hz, 1 F, F-7) ppm. $C_9H_5F_3N_2O_3$ (246.14): calcd. C 43.92, H 2.05, N 11.38; found C 44.42, H 2.27, N 10.88.

Ethyl 4,5,7-Trifluoro-3-hydroxy-1*H*-indazole-6-carboxylate (9): Hydrazine monohydrate (98%, 5.0 mmol, 250 mg) was added to a solution of diethyl 2,3,5,6-tetrafluoroterephthalate (**24**, 2.4 mmol, 700 mg) in toluene (30 mL) in a three-necked, round-bottomed flask. The mixture was heated at reflux for 24 h and was then allowed to cool to room temperature. The precipitate formed was filtered and dissolved in a saturated sodium hydrogen carbonate solution (10 mL), which was extracted with diethyl ether (3 × 20 mL). The organic fractions were combined and dried with anhydrous sodium sulfate. This solution was combined with the mother liquor and solvents were removed under reduced pressure. The resulting residue was then chromatographed (hexane/diethyl ether 1:1) to recover most of the unreacted starting ester and to provide the pure product (100 mg, yield 16%); m.p. 236.0 °C (DSC). ^{1}H NMR ([D$_6$]DMSO, 400 MHz): δ = 12.9 (br. s, 1 H, N*H*), 11.4 (br. s, 1 H, O*H*), 1.31 (t, ^3J = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 4.40 (q, ^3J = 7.1 Hz, 2 H, $CO_2CH_2CH_3$) ppm. ^{13}C NMR ([D$_6$]-DMSO, 100 MHz): δ = 154.5 (m, C-3), 104.2 (dd, ^2J = 19.4, ^3J = 5.7 Hz, C-3a), 138.6 (ddd, ^1J = 250.5, ^2J = 14.7, ^4J = 4.9 Hz, C-4), 138.1 (ddd, ^1J = 242.4, ^2J = 13.8, ^3J = 3.8 Hz, C-5), 108.8 (dd, ^2J = 18.8, ^2J = 15.1 Hz, C-6), 140.4 (ddd, ^1J = 254.1, ^3J = 6.3, ^4J = 3.8 Hz, C-7), 128.6 (dd, ^2J = 17.6, ^3J = 6.8 Hz, C-7a), 14.0 (s, $CO_2CH_2CH_3$) 62.3 (s, $CO_2CH_2CH_3$), 160.4 (s, $CO_2CH_2CH_3$) ppm. ^{19}F NMR ([D$_6$]DMSO, 376 MHz): δ = –150.6 (dd, $^3J_{F-5}$ = 21.1, $^5J_{F-7}$ = 21.1 Hz, 1 F, F-4), –153.8 (dd, $^3J_{F-4}$ = 21.1, $^4J_{F-7}$ = 3.9 Hz, 1 F, F-5) –133.8 (dd, $^5J_{F-4}$ = 21.1, $^4J_{F-5}$ = 3.9 Hz, 1 F, F-7) ppm. $C_{10}H_7F_3N_2O_3$ (260.17): calcd. C 46.16, H 2.71, N 10.77; found C 46.05, H 2.83, N 10.63.

4,5,6-Trifluoro-3-hydroxy-1*H*-indazole-7-carboxylic Acid (10): A solution of ethyl 4,5,6-trifluoro-3-hydroxy-1*H*-indazole-7-carboxylate (**12**, 0.54 mmol, 140 mg) and sodium hydroxide (1.8 mmol, 70 mg) in water (5 mL) was stirred at room temperature for 24 h. Concentrated hydrochloric acid was then added to reach pH 1 and the solution was cooled to 4 °C for a further 24 h. After filtration of the precipitate, the pure product was collected (120 mg, yield 96%). A similar procedure was used to obtain **10** from **11**; m.p. >300 °C (microscope). ^{1}H NMR ([D$_6$]DMSO, 400 MHz): δ = 11.92 (s, 1 H, N*H*), 11.2 (br. s, 1 H, O*H*) ppm. ^{13}C NMR ([D$_6$]-DMSO, 100 MHz): δ = 154.0 (s, C-3), 98.5 (d, ^2J = 16.3 Hz, C-3a), 145.6 (ddd, ^1J = 260.4, ^2J = 11.5, ^3J = 5.5 Hz, C-4), 133.1 (ddd, ^1J = 238.5, ^2J = 18.5, ^2J = 13.9 Hz, C-5), 152.2 (ddd, ^1J = 261.1, ^2J = 13.5, ^3J = 2.8 Hz, C-6), 98.2 (dd, ^2J = 11.3, ^3J = 3.8 Hz, C-7), 136.2 (dd, ^3J = 9.1, ^3J = 6.7 Hz, C-7a), 163.4 (s, CO_2H) ppm. ^{19}F NMR ([D$_6$]DMSO, 376 MHz): δ = –135.1 (dd, $^3J_{F-5}$ = 21.7, $^4J_{F-6}$ = 12.7 Hz, 1 F, F-4), –172.5 (dd, $^3J_{F-4}$ = 21.7, $^3J_{F-6}$ = 21.7 Hz, 1 F, F-5), –128.4 (br. s, 1 F, F-6) ppm. $C_8H_3F_3N_2O_3$ (232.12): calcd. C 41.40, H 1.30, N 12.07; found C 41.09, H 1.52, N 11.61.

Methyl 4,5,6-Trifluoro-3-hydroxy-1*H*-indazole-7-carboxylate (11) and Methyl 4,6,7-Trifluoro-3-hydroxy-1*H*-indazole-5-carboxylate (5): A solution of dimethyl 2,4,5,6-tetrafluoroisophthalate (**20**, 1.8 mmol, 470 mg) in toluene (20 mL) was heated to 60 °C in a three-necked, round-bottomed flask, and hydrazine monohydrate (98%, 3.5 mmol, 175 mg) was then added dropwise. The mixture was heated at reflux for 16 h and was then allowed to cool to room temperature. The resulting mixture of compounds was chromatographed (hexane/diethyl ether 4:1 to neat diethyl ether) to provide first **11** (160 mg, yield 37%) and then **5** (120 mg, yield 28%); m.p. 265.7 °C (DSC). ^{1}H NMR ([D$_6$]DMSO, 400 MHz): δ = 12.19 (s, 1 H, N*H*), 11.4 (br. s, 1 H, O*H*), 3.91 (s, 3 H, CO_2CH_3) ppm. ^{13}C NMR ([D$_6$]DMSO, 100 MHz): δ = 154.1 (m, C-3), 98.3 (d, ^2J = 16.3 Hz, C-3a), 145.9 (ddd, ^1J = 261.2, ^2J = 11.3, ^3J = 5.0 Hz, C-4), 133.1 (ddd, ^1J = 238.3, ^2J = 18.2, ^2J = 14.4 Hz, C-5), 152.2 (ddd, ^1J = 262.5, ^2J = 13.2, ^3J = 3.2 Hz, C-6), 97.3 (dd, ^2J = 10.4, ^3J = 4.5 Hz, C-7), 135.5 (dd, ^3J = 10.1, ^3J = 6.3 Hz, C-7a), 52.3 (s, CO_2CH_3), 161.9 (s, CO_2CH_3) ppm. ^{19}F NMR ([D$_6$]DMSO, 376 MHz): δ = –133.9 (dd, $^3J_{F-5}$ = 21.9, $^5J_{F-6}$ = 13.4 Hz, 1 F, F-4), –172.3 (dd, $^3J_{F-4}$ = 21.9, $^3J_{F-6}$ = 21.9 Hz, 1 F, F-5), –128.5 (br. dd, 1 F, F-6) ppm. $C_9H_5F_3N_2O_3$ (246.14): calcd. C 43.92, H 2.05, N 11.38; found C 43.90, H 2.21, N 11.24.

Ethyl 4,5,6-Trifluoro-3-hydroxy-1*H*-indazole-7-carboxylate (12): A solution of diethyl 2,4,5,6-tetrafluoroisophthalate (**21**, 1.7 mmol, 500 mg) in toluene (25 mL) was heated to 60 °C in a three-necked, round-bottomed flask, and hydrazine monohydrate (98%, 4.0 mmol, 200 mg) was then added dropwise. The mixture was stirred at 60–65 °C for 18 h. The precipitate formed was filtered while the solution was still hot. The resulting solid was purified by column chromatography (hexane/diethyl ether 2:1) to provide **12** (270 mg, yield 61%); m.p. 257.5 °C (DSC). ^{1}H NMR ([D$_6$]DMSO, 400 MHz): δ = 12.1 (br. s, 1 H, N*H*), 11.3 (br. s, 1 H, O*H*), 1.33 (t, ^3J = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 4.41 (q, ^3J = 7.1 Hz, 2 H, $CO_2CH_2CH_3$) ppm. ^{13}C NMR ([D$_6$]DMSO, 100 MHz): δ = 154.1 (m, C-3), 98.3 (d, ^2J = 16.3 Hz, C-3a), 145.8 (ddd, ^1J = 261.4, ^2J = 12.1, ^3J = 5.9 Hz, C-4), 133.1 (ddd, ^1J = 238.6, ^2J = 18.2, ^2J = 13.2 Hz, C-5), 152.4 (ddd, ^1J = 261.8, ^2J = 13.2, ^3J = 3.1 Hz, C-6), 97.5 (dd, ^2J = 11.5, ^3J = 4.7 Hz, C-7), 135.6 (dd, ^3J = 10.0, ^3J = 6.3 Hz, C-7a), 14.2 (s, $CO_2CH_2CH_3$), 61.3 (s, $CO_2CH_2CH_3$), 161.7 (s, $CO_2CH_2CH_3$) ppm. ^{19}F NMR ([D$_6$]DMSO, 376 MHz): δ = –134.1 (dd, $^3J_{F-5}$ = 20.7, $^4J_{F-6}$ = 13.8 Hz, 1 F, F-4), –172.3 (dd, $^3J_{F-4}$ = 20.7, $^3J_{F-6}$ = 20.7 Hz, 1 F, F-5), –128.0 (dd, $^3J_{F-5}$ = 20.7, $^4J_{F-4}$ = 13.8 Hz, 1 F, F-6) ppm. $C_{10}H_7F_3N_2O_3$ (260.17): calcd. C 46.16, H 2.71, N 10.77; found C 46.08, H 2.81, N 10.73.

Acknowledgments

This research has been financed by the Ministerio de Educación y Ciencia (MEC) of Spain, CTQ2007-62113 project. Dr. Ibon Alkorta's scientific help is greatly appreciated.

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Received: September 28, 2009
Published Online: December 22, 2009

