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Simple preparations of 4 and 5-iodinated pyrazoles as useful building blocks

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ABSTRACT

The pyrazole nucleus has recently become a recurrent scaffold in the research fields of CropScience and oncology. We report here the preparation of an array of 4- and 5-iodinated pyrazole derivatives, such as 4-iodo-3-trifluoromethylpyrazole or ethyl 5-iodo-4-carboxy-3-trifluoromethylpyrazoles. This work provide access to many new pyrazole derivative, including 11 original out of 16 iodinated building blocks, thus opening accesses to new chemical entities featuring a pyrazole nucleus.

1. Introduction

Pyrazole chemistry[1,2] is currently enjoying the focus of renewed research[3–20] aiming at developing accesses to original derivatives of potential interest, for instance in the research fields of CropScience[21,22] or oncology.[23–29] We recently reported on the synthesis of 5-iodo-3-ethoxypyrazoles as original building blocks for the preparation of whole arrays of new chemical entities.[30] We wish to report here preparations of many additional 4 or 5-iodinated as well as 4,5-diiodopyrazoles derivatives. These compounds are obvious building blocks, which should open accesses to even more new chemical entities featuring a pyrazole nucleus.

Table 1 sums up the iodination of pyrazoles **1a**–**f**, their preparation was either reported elsewhere[31–34] or, for compound **1f**, an improved one is described in the experimental part. As for many pyrazoles,[35] the 4-iodinations of 3-alkoxypyrazoles, such as **1a**–**c** were very easily achieved with iodine under mild basic conditions leading to compounds **2a** and **2c**.[36,37] Accordingly, with the same reaction conditions, we also prepared compound **2b** or the 5-trifluoromethyl-bearing homologue **2d** both in 90% yield. On the other hand, attempts to iodinated the 3-trifluoromethylpyrazoles **1e**–**f** on carbon 4 with these conditions completely failed. This pointed out that these electron-poor substrates called for rather stronger reaction conditions. A literature search showed that the 4-iodination of 3-trifluoromethylpyrazole (**1e**) can be achieved with a mixture of cerium ammonium nitrate and iodine.[38,39] For our part, we found that the electron-poor 3-trifluoromethylpyrazole **1e** and its 5-phenyl homologue **1f** were most conveniently iodinated with *N*-iodosuccinimide (NIS) in 50% sulfuric acid.[40–43] With these conditions we could prepare compounds **2e** and **2f** both in 85% yield. However, from compound **1f**, the occurrence of a small proportion of a bis-iodinated byproduct could not be avoided.

With the use of NIS and heat under neutral conditions, the 5-iodination of alkoxypyrazoles was generalized to many substrates, such as compound **3b**–**e**. Again, the synthesis of the starting materials can be found in the experimental part. Compared to our previous results,[30] switching from cyclohexane to refluxing dichloroethane actually led to a substantial improvement (from 60 to 82% yield) especially in the case of large scale preparation of **4a**.[30]

Table 1
4-Iodination of pyrazoles **1a**–**f**

	R3	R5	Yield %	Conditions
a	EtO	H	91	I_2, NaI, K_2CO_3, EtOH/H_2O
b	EtO	Me	90	I_2, NaI, K_2CO_3, EtOH/H_2O
c	EtO	Ph	75	I_2, NaI, K_2CO_3, EtOH/H_2O
d	EtO	CF_3	90	I_2, NaI, K_2CO_3, EtOH/H_2O
e	CF_3	H	85	NIS, H_2SO_4 50% v/v, 20 °C
f	CF_3	Ph	85	NIS, H_2SO_4 50% v/v, 20 °C

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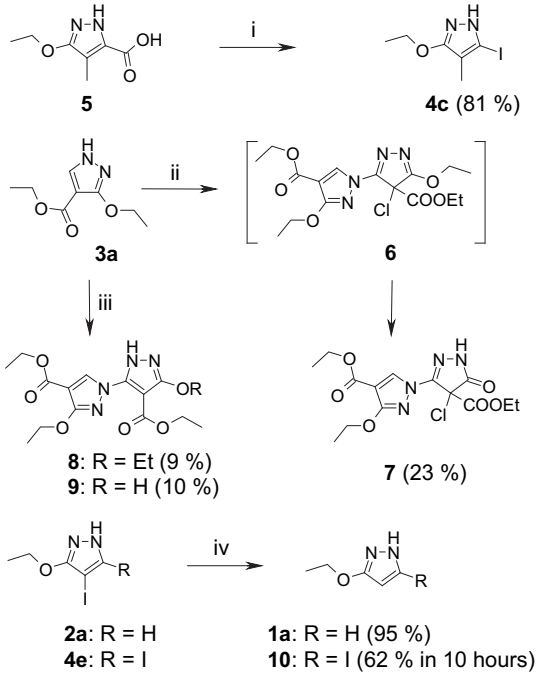
The reaction could also be run in a closed vessel using a microwave oven, which allowed to heat beyond the boiling point and thus shortened the reaction duration. Some difficulties were encountered with the iodination of the 4-phenyl derivative **3d** as polyiodination sometime marred the reaction. The best yield in this case (66%) was obtained in refluxing dichloroethane and was accompanied by the recovery of 14% of the starting material **3d**. Attempts to 5-brominated compound **3d** were far less successful,[44] in accord with the extensive side-ring polybromation reported for other examples.[45–48] The 4,5-diodopyrazole **4e** was also easily obtained from the 4-iodopyrazole **2a**/**3e** or, rather more simply, directly from compound **1a** under the same reaction conditions by doubling the amount of NIS. Again, the 3-triflurometylpyrazoles **3f**–**j** were far less reactive. The 5-iodination of **3i**, has been reported in an unspecified yield and required the use of [bis(trifluoroacetoxy)iodo]benzene and iodine.[49] However, the fairly high temperature accessible with a microwave oven allowed the synthesis of the 5-iodinated pyrazoles **4f**–**j** just with the use of NIS. Interestingly, if some polyiodination was noted for the electron-rich 3-ethoxy-4-phenyl-pyrazole (**3d**), it was not the case with the 3-trifluoromethyl-4-phenylpyrazole (**3h**). With this method, we could also prepare the 4,5-diiodo derivative **4j** albeit from the 4-iodopyrazole **2e**/**3j** only. Indeed, contrary to the preparation of the diiodo derivative **4e** attempts to mono or bis-iodinated 3-triflurometh ypyrazole (**1e**) with NIS at high temperature failed as no reaction was observed. More unexpectedly, chlorination of **1e**, with *N*-chlorosuccinimide under the same conditions, was possible and led to the 4-chloropyrazole **3i** in a 73% yield (see experimental part) (Table 2).

Table 2
5-Iodination of pyrazoles **3a**–**j**

3a-j **4a-j**

	R3	R4	Yield %	Conditions
a	EtO	CO_2Et	82	NIS, $ClCH_2CH_2Cl$, reflux
b	EtO	CN	74	NIS, $ClCH_2CH_2Cl$, MW, 150 °C
c	EtO	CH_3	72	NIS, $ClCH_2CH_2Cl$, reflux
d	EtO	Ph	66	NIS, $ClCH_2CH_2Cl$, reflux
e	EtO	I	85	NIS, $ClCH_2CH_2Cl$, reflux
f	CF_3	CO_2Et	56	NIS, $ClCH_2CH_2Cl$, MW, 190 °C
g	CF_3	CH_3	90	NIS, $ClCH_2CH_2Cl$, MW, 140 °C
h	CF_3	Ph	82	NIS, $ClCH_2CH_2Cl$, MW, 140 °C
i	CF_3	Cl	54	NIS, $ClCH_2CH_2Cl$, MW, 190 °C
j	CF_3	I	85	NIS, $ClCH_2CH_2Cl$, MW, 190 °C

The preparation of compound **4c** was actually achieved in a better 81% yield from acid **5**. This approach involved a remarkable iododecarboxylation reaction in the presence of an anionic surfactant, which was previously reported for the triiodination of 3-pyrazole carboxylic acid.[50] With this method, we also avoided the low yielding preparations of **3c**, either by decarboxylation of **5** or by the condensation of hydrazine hydrochloride with ethyl 2-methyl-3-oxopropanoate.[51] We also attempted the 5-chlorination of **3a** with *N*-chlorosuccinimide (NCS), which could have led in a few steps to the preparation of 5-chloro-4-iodo-3-ethoxypyrazole. Quite unexpectedly, at 130 °C, we could isolate from the reaction products the dimeric derivative **7**. Its occurrence is actually reminiscent of trimeric structures reported in the past in the course of the preparation of simple 3-halogenopyrazoles.[52–58] Mechanistically-wise, we suggest the hydrolysis of the 4-chlorinated ethoxypyrazole moiety of intermediate **6** upon work-up of the reaction, which would release much of the 4*H*-pyrazole ring strain (the 4-chlorination could also take place after this step).[54] The ^1H NMR spectra of a trial at room temperature also pointed out the occurrence of compound **7** along with a mixture of other products. The reductive treatment[59] of the crude reaction extract with sodium sulfite in a boiling mixture of water and THF led, with an important loss of material, to the isolation of the two additional products **8** and **9**. The structure elucidation of these compounds, resulting from the reduction of **6** and **7**, further confirmed the mechanistic process suggested above. Another series of unexpected reactions were also observed in the course of this study. Thus, the iodine on carbon 4 of compound **2a** turns out to be quite labile as its completed reduction, along with iodine (or iodinemonochloride) evolution, was achieved in boiling 2 N hydrochloric acid in the course of 90 min. Control experiments demonstrated that both acidic conditions and the presence of oxygen are crucial for this reaction to proceed. A similar and specific reduction of the 4,5-diiodo derivative **4e** into the known[30] 5-iodopyrazole **10** also took place although far more slowly as a 62% conversion was observed after 10 h of reflux. These results are reminiscent of the reported regioselective carbon 4 reduction of the 3,4-diiodo-5-methylpyrazoles or 3,4,5-triodopyrazole. Such reductions were achieved by using either triethylamine trihydrofluoride or hydrogen fluoride although the reductions were apparently run in closed vessels.[50,60] Attempts to reduce the 4,5-diiodo-3-trifluoromethyl **4j** under the same reaction conditions only pointed out a very slow reduction rate as this compound is readily removed from the reaction mixture into the condenser by steam-extraction (Scheme 1).



5 **4c** (81 %)
3a **6**
8: R = Et (9 %)
9: R = H (10 %)
7 (23 %)
2a: R = H
4e: R = I
1a: R = H (95 %)
10: R = I (62 % in 10 hours)

Scheme 1. i: NaOH, $CH_3(CH_2)_{11}C_6H_4SO_3Na$, I_2, H_2O. ii: NCS, dichloroethane, 130 °C iii: (a) NCS, dichloroethane, 20 °C (b) Na_2SO_3, THF/H_2O reflux. iv: 2 N HCl, air, reflux.

In conclusion, the simple preparations of the 4- and 5-iodinated pyrazoles described in this work should be useful for the synthesis of a vast array of more elaborated derivatives with the use of carbon–carbon or carbon–heteroatom coupling reactions. We should actually report on the palladium-catalyzed transformations of some of these building blocks in the near future. Moreover, the selective labile character of the iodine atom on C-4 observed for compound **4e** may help in designing regioselective transformations of such 4,5-diiodopyrazoles.

2. General methods

A Biotage initiator 2 microwave oven was used for reactions mentioning such heating method. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer at 400 MHz and 100 MHz, respectively. Shifts (δ) are given in parts per million with respect to the TMS signal and coupling constants (J) are given in hertz. Column chromatography were performed either on Merck silica gel 60 (0.035–0.070 mm) or neutral alumina using a solvent pump and an automated collecting system driven by a UV detector set to 254 nm unless required otherwise. Sample deposition was carried out by absorption of the mixture to be purified on a small amount of the solid phase followed by its deposition of the top of the column. The low resolution mass spectra were obtained on an Agilent 1100 series LC/MSD system using an atmospheric electrospray ionization system and the high resolution mass spectra (HRMS) were obtained using a Waters Micromass Q-Tof with an electrospray ion source. Preparations and characterization of compounds **2a**,[30] **2c**,[30] **3c**,[51] **8**[30] and **10**[30] have been reported previously.

2.1. 5-Phenyl-3-(trifluoromethyl)-1*H*-pyrazole (1f)

4,4,4-Trifluoro-1-phenylbutane-1,3-dione (7.1 g, 0.032 mol) and hydrazine hydrate (1.75 mL, 0.036 mol) were refluxed in ethanol (140 mL) for 2 h. The reaction mixture was concentrated to dryness to yield 3-phenyl-5-(trifluoromethyl)-4,5-dihydro-1*H*-pyrazol-5-ol.[61] ^{1}H NMR (DMSO-d_6): 3.40 (d, 1H, J=18.0 Hz); 3.37 (d, 1H, J=18.0 Hz); 7.39 (m, 4H); 7.64 (m, 2H); 7.93 (s (br), 1H). ^{13}C NMR (DMSO-d_6): 41.3; 91.1 (J=30 Hz); 124.1(J=280 Hz); 125.5; 128.5; 129.0; 132.2; 147.4. This compound was then boiled in 2 N hydrochloric acid (40 mL) for 1 min. After cooling, the precipitate was filtered, washed with water and dried under vacuum to yield compound **1f** as a white solid (6.91 g, 98%) with analytical data identical to the reported one.[62,63]

2.2. Iodination of 1b and 1d

The considered alkoxypyrazole (57 mmol), sodium iodide sodium iodide (8.6 g, 57 mmol) and potassium carbonate (23.8 g, 1.7 mmol) were dissolved in a 4:1 water/ethanol mixture (250 mL). Iodine (19 g, 74 mmol) was added and the suspension was stirred for 1 h. The mixture was treated with sodium sulfite, diluted with brine (500 mL) and the resulting white precipitate was filtered. This was washed with water and dried under vacuum at 80 °C until all the byproduct triiodomethane has sublimed to yield compounds **2b** or **2d** as described below.

2.3. 3-Ethoxy-4-iodo-5-methyl-1*H*-pyrazole (2b)

Obtained as an off-white solid in 90% yield; mp 104 °C ^{1}H NMR ($CDCl_3$): 1.40 (t, 3H, J=7.0 Hz); 2.22 (s, 3H); 4.26 (q, 2H, J=7.0 Hz); 10.10 (s (br), 1H). ^{13}C NMR ($CDCl_3$): 12.1; 14.8; 46.5; 65.1; 142.6; 163.2. HRMS: calcd for $C_6H_9IN_2O$+H: 252.9838; Found: 252.9788.

2.4. 3-Ethoxy-4-iodo-5-(trifluoromethyl)-1*H*-pyrazole (2d)

Obtained as a white solid in 90% yield; mp 125 °C ^{1}H NMR ($CDCl_3$): 1.45 (t, 3H, J=7.0 Hz); 4.33 (q, 2H, J=7.0 Hz); 9.5 (s (br), 1H). ^{13}C NMR ($CDCl_3$): 14.6; 44.4; 66.8; 119.0 (q, J=268 Hz); 136.4 (q, J=39 Hz); 162.3. HRMS: calcd for $C_6H_6F_3IN_2O$+H: 306.9555; Found: 306.9557.

2.5. Iodination of compound 1e and 1f

The considered 3-trifluoromethylpyrazole (68 mmol) was dissolved in 50% aqueous sulfuric acid (20 mL). This was cooled to 0 °C and *N*-iodosuccinimide (18.5 g, 82 mmol) was added. The suspension was stirred 10 min at 0 °C and then stirred, 3 h for **1e** and two days for **1f**, at room temperature. This was dispersed in water (500 mL) and stirred overnight. The precipitate was filtered, washed with water and redispersed in boiling water (400 mL), a small amount of sodium disulfite was added and the suspension was left to cool, filtered again and dried under vacuum to yield compound **2e** or **2f** as described below.

2.6. 4-Iodo-3-(trifluoromethyl)-1*H*-pyrazole (2e)

Obtained as a white solid in 85% yield; mp 141 °C ^{1}H NMR ($CDCl_3$): 7.80 (s, 1H); 13.1 (s (br), 1H). ^{13}C NMR ($CDCl_3$): 54.4; 121.0 (q, J=268 Hz); 136.9; 143.9 (q, J=39 Hz). HRMS: calcd for $C_4H_2F_3IN_2$–H: 260.9137; Found: 260.9126.

2.7. 4-Iodo-5-phenyl-3-(trifluoromethyl)-1*H*-pyrazole (2f)

Obtained as a white solid in 85% yield still containing 1% of unreacted pyrazole **1f** and 4% of a bis-iodinated material. A sample was triturated (with losses) in boiling dichloromethane for analytical purposes; mp 177 °C ^{1}H (DMSO-d_6): 7.48–7.57 (m, 3H); 7.67–7.70 (m, 2H); 14.24 (s (br), 1H). ^{13}C (DMSO-d_6): 57.0; 121.9 (J=269 Hz); 128.5; 128.9; 129.2; 130.0; 143.7 (J=39 Hz); 146.5. HRMS: calcd for $C_{10}H_6F_3IN_2$–H: 336.9450; Found: 336.9409.

2.8. 3-Ethoxy-1*H*-pyrazole-4-carbonitrile (3b)

This compound was prepared from **3a**[30] in two steps as follow. Step 1: in a 400 mL steel reactor, compound **3a** (48.7 g, 0.26 mol) and ammonium chloride (3.6 g, 0.066 mol)[64–66] were mixed with 32% ammonia (200 mL, 3.31 mol). The reactor was closed and heated to 80 °C for 29 h. After cooling back to room temperature, the solution was concentrated to dryness under vacuum. The resulting dry solid was suspended in a 1/1 mixture of dichloromethane and toluene (300 mL), filtered and the collected solid dried under vacuum at 70 °C to yield 38.11 g of 3-ethoxy-1*H*-pyrazole-4-carboxamide as white solid (34.51 g, 84%, taking into account the 3.6 g of ammonium chloride that could be present in this solid). The NMR analysis of the filtrate (5.78 g when concentrated to dryness) showed the presence of some decarboxylated material,[30] some unreacted ester and a small amount of the amide. A sample was recrystallized in a small amount of water with much loss for analytical purposes; mp 168 °C ^{1}H (DMSO-d_6): 1.35 (t, 3H, J=7.0 Hz); 4.26 (q, 2H, J=7.0 Hz); 6.56 (s (br), 1H); 7.00 (s (br), 1H); 7.91 (s, 1H). ^{13}C (DMSO-d_6): 15.1; 65.0; 102.4; 133.1; 160.0; 163.6. HRMS: calcd for $C_6H_9N_3O_2$+H: 156.0773. Exptl: 156.0749. Step 2: in a flask protected from moisture by a calcium chloride guard, 3-ethoxy-1*H*-pyrazole-4-carboxamide (20.3 g, 0.130 mol) was dissolved in acetonitrile (300 mL, dried over 4 Å molecular sieve). Phosphorus oxychloride (26.8 mL, 0.287 mol) was added and the mixture was heated to reflux for 4.5 h. The resulting dark mixture was poured onto 600 g of ice with stirring. After decomposition of phosphorus oxychloride, the mixture was made basic with 20% ammonia, saturated with sodium chloride and extracted three times with ethyl acetate. The organic phase was dried over magnesium sulfate and concentrated to dryness to yield crude compound **3b**. This solid was extracted with boiling isopropyl ether (three time 300 mL) and filtered. The filtrate was concentrated to dryness to yield compound **3b** as a yellow powder still containing a small proportion of water (13.96 g, 77%). A small sample (from a less clean batch) could be purified by a chromatography over silica gel (cyclohexane/dichloromethane from 1/2 to 1/1); mp 102 °C ^{1}H ($CDCl_3$): 1.46 (t, 3H, J=7.1 Hz); 4.37 (q, 2H, J=7.1 Hz); 7.79 (s, 1H); 10.15 (s (br), 1H). ^{13}C ($CDCl_3$): 14.6; 66.0; 79.0; 112.9; 135.0; 163.9. This compound did not ionize under the HRMS conditions.

2.9. 4-Phenyl-3-ethoxy-1*H*-pyrazole (3d)

This compound was prepared in two step as follow. Step 1 compound **1a** (2.06 g, 8.65 mmol) was dissolved in ethyl acetate (150 mL), triethylamine (1.9 mL, 13.8 mmol; dried over 4 Å molecular sieves) was added followed by mesylchloride (1.0 mL, 13.0 mmol). The solution was protected from moisture by a calcium chloride guard and stirred for 2 h at room temperature. This was washed with 2 N potassium carbonate, 0.5 N hydrochloric acid and brine, dried over sodium sulfate and concentrated to dryness to yield the 2/5 mixture of the two isomers 5-ethoxy-4-iodo-1-(methylsulfonyl)-1*H*-pyrazole and 3-ethoxy-4-iodo-1-(methylsulfonyl)-1*H*-pyrazole as an oil that slowly solidified (2.68 g, 98%). ^{1}H ($CDCl_3$): 1.45 (d, 5/7 of 3H, J=7.1 Hz); 1.49 (d, 2/7 of 3H, J=7.1 Hz); 3.25 (s, 5/7 of 3H); 3.31 (s, 2/7 of 3H); 4.41 (m, 2H); 7.61 (s, 2/7 of 1H); 7.90 (s, 5/7 of 1H). m/z (LC/MS)=253. Step 2: in a 10 mL biotage-adapted tube, the mixture of the mesyl-protected pyrazoles (1.38 g, 4.37 mmol), phenyl boronic acid (0.7 g, 5.68 mmol), caesium carbonate (3.56 g; 10.9 mmol) were dispersed in a mixture of propanol (3 mL) and water (2 mL). The oxygen was removed by a slow stream of argon and [1,1′-bis(diphenylphosphino)ferrocene] dichloropalladium complexed with dichloromethane (0.178 g, 0.218 mmol) was then added before sealing the tube. This was heated in the microwave oven for 40 min at 120 °C. This was diluted in water, extracted with ethyl acetate; the organic layer was washed with brine and dried over sodium sulfate and concentrated to dryness. The residue was dissolved in ethanol (150 mL) and potassium hydroxide (0.8 g) this was heated at 90 °C for 2 h. This was diluted in water, made slightly acid with ammonium chloride, extracted with ethyl acetate, the organic layer was washed with brine and dried over sodium sulfate and concentrated to dryness. The resulting residue was purified by a chromatography over neutral alumina containing 1.5% of water (dichloromethane/ethanol 99/1) and the corresponding fraction was further purified by a recrystallisation in cyclohexane to yield compound **3d** (57%) as a white powder; mp 176 °C ^{1}H ($CDCl_3$): 1.49 (t, 3H, J=7.0 Hz); 4.39 (q, 2H, J=7.0 Hz); 7.23 (m, 1H); 7.38 (m, 2H); 7.66 (s, 1H); 7.68 (m, 2H); 9.16 (s (br.), 1H). ^{13}C ($CDCl_3$): 14.9; 64.7; 107.2; 125.8; 125.9; 127.0; 128.5; 131.9; 160.7. HRMS: calcd for $C_{11}H_{12}N_2O$+H: 189.1028. Found: m/z, 189.0984.

2.10. Ethyl 3-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (3f)

Hydrazine hydrate (10 g, 0.199 mol) was dissolved in ethanol (400 mL). This was cooled to 0 °C and a solution of ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate (47.03 g, 0.19 mol) in ethanol (200 mL) was added drop-wise over 90 min at 0 °C. The solution was left to warm to room temperature for 3 h and concentrated to dryness. The residue was dispersed in boiling cyclohexane (200 mL) and left to cool to room temperature. The precipitate was filtered, washed with cyclohexane and dried under vacuum at 75 °C to yield compound **3f** as a yellow powder (38.67 g, 95%); mp 145 °C ^{1}H NMR ($CDCl_3$): 1.40 (t, 3H, J=7.0 Hz); 4.39 (q, 2H, J=7.0 Hz); 8.26 (s, 1H); 13.2 (s (br), 1H). ^{13}C NMR ($CDCl_3$): 14.0; 61.2; 113.4; 121.0 (q, J=268 Hz); 135.3; 142.0 (q, J=38 Hz); 160.8. HRMS: calcd For $C_7H_7F_3N_2O_2$−H: 207.0381; Found: 207.0377.

2.11. 4-Methyl-3-(trifluoromethyl)-1*H*-pyrazole (3g)

In a moisture-protected atmosphere at 0 °C, trifluoroacetic anhydride (13.2 mL, 0.0949 mol) was added drop-wise to a mixture of the isomers of 1-ethoxyprop-1-ene (8.1 g, 0.094 mol) in dry pentane (60 mL). This was stirred at 0 °C for 2 h and at 20 °C for 24 h. The ^{1}H NMR spectra of a sample pointed out the occurrence of a diastereoisomeric mixture of 1-ethoxy-4,4,4-trifluoro-2-methyl-3-oxobutyl 2,2,2-trifluoroacetate, which did not spontaneously eliminate trifluoroacetic acid, contrary to the reaction between vinylether and trifluoroacetic anhydride, previously described under the same conditions.[34] In any case, this solution was cooled to 0 °C and hydrazine hydrate (5.47 mL, 0.11 mol) diluted in ethanol (50 mL) was added drop-wise. The resulting solution was concentrated to dryness and the residue dispersed in water (400 mL). The white precipitate was filtered, washed with water and dried in open air before a recrystallisation in cyclohexane (three crops), which yielded compound **3g** as a white powder (7.54 g, 53%); mp 105 °C ^{1}H NMR ($CDCl_3$): 2.23 (s, 3H); 7.49 (s, 1H); 12.9 (s (br), 1H). ^{13}C NMR ($CDCl_3$; D1 set at 10s): 7.8; 114.8; 122.3 (q, J=269 Hz); 129.7; 140.2 (q, J=36 Hz). HRMS: calcd for $C_5H_5F_3N_2$+H: 151.0483; Found: 151.0497.

2.12. 4-Chloro-3-(trifluoromethyl)-1*H*-pyrazole (3i)

From the indications on page 343 of Ref. 49, the following procedure was designed: 3-(trifluoromethyl)-1*H*-pyrazole[32–34] (**1e**) (5.54 g, 40.7 mol) and *N*-chlorosuccinimide (5.97 g, 44.7 mmol) in acetonitrile (13 mL) were heated in a microwave oven at 120 °C for 1 h. The resulting mixture was concentrated to dryness and dispersed in water (300 mL). The precipitate was filtered, rinsed with water and left to dry over 3 days to yield compound **3i** (5.08 g, 73%) as a powder; mp 94 °C ^{1}H NMR ($CDCl_3$): 7.69 (s, 1H); 11.2 (s (br), 1H). ^{13}C NMR ($CDCl_3$): 109.6; 120.2 (q, J=267 Hz); 129.5; 130.0 (q, J=37 Hz). HRMS: calcd for $C_4H_2ClF_3N_2$−H: 168.9780; Found: 168.9747.

2.13. Ethyl 3-ethoxy-5-iodo-1*H*-pyrazole-4-carboxylate (4a)

Compound **3a** (70 g, 0.386 mol) and 95% *N*-iodosuccinimide (100.6 g, 0.418 mol) were boiled in dichloroethane (700 mL) for 17 h under an inert atmosphere. While stirring, water (100 mL) was added to the cooled solution followed by powdered sodium disulfite until disappearance of the purple colour. This was decanted, the organic layer was washed four times with water (150 mL) once with a saturated sodium hydrogenocarbonate solution (100 mL) and dried over magnesium sulfate before concentration to dryness. The resulting yellow solid was dispersed in 1 N hydrochloric acid (500 mL) at room temperature, filtered, washed thoroughly with water and dried under vacuum at 35 °C to yield compound **4a** (96.6 g, 82%) featuring analytical data identical with the previously reported one.[30]

2.14. 5-Ethoxy-3-iodo-1*H*-pyrazole-4-carbonitrile (4b)

Compound **3b** (2.5 g, 0.018 mol) and *N*-iodosuccinimide (4.5 g, 0.020 mol) were heated in a microwave oven in dichloroethane (15 mL) at 150 °C for 1 h. The resulting purple solution was diluted in ethyl acetate and decolorized with a sodium disulfite solution. The organic layer was washed five times with brine, dried over magnesium sulfate and concentrated to dryness. The residue (4.5 g) was purified by a chromatography over silica gel (cyclohexane/ethyl acetate 2.5/1) to yield compound **4b** as a slightly yellow powder (3.56 g, 74%); mp 147 °C ^{1}H (DMSO-d_6): 1.30 (t, 3H, J=7.0 Hz); 4.24 (q, 2H, J=7.0 Hz); 13.4 (s (br), 1H). ^{13}C (DMSO-d_6, D1 set to 10s): 14.4; 65.1; 85.5; 91.9; 113.5; 163.9. HRMS: calcd for $C_6H_6IN_3O$+H: 263.9634. Exptl: 263.9581.

2.15. 3-Ethoxy-5-iodo-4-methyl-1*H*-pyrazole (4c)

Compound **3c** (0.65 g, 0.0051 mol) *N*-iodosuccinimide (1.22 g, 0.0054 mmol) were refluxed in dichloroethane (40 mL) under an inert atmosphere for 2h. This was diluted in ethyl acetate, washed with a solution of sodium sulfite, with brine, dried over magnesium sulfate and concentrated to dryness. The residue was purified by a chromatography over silica gel (cyclohexane/ethyl acetate 4/1) to

yield compound **4c** (0.94 g, 72%). Alternative procedure from **5**: In an oversized flask (500 mL), compound **5** (2.73 g, 0.016 mol), sodium hydroxide (0.55 g, 0.0162 mol), sodium dodecylbenzenesulfonate (0.048 g, 0.14 mmol) were dissolved in boiling water (50 mL). Upon dissolution, iodine (4.11 g, 0.0162 mol) was added portion-wise to avoid over-foaming of the solution. The resulting suspension was then heated for three more hours, this was diluted in boiling water (100 mL) decolorized with a solution of sodium sulfite and left to cool under stirring. The precipitate was filtered, washed with water and dried to yield compound **4c** (3.28 g, 81%) as an off-white solid; mp 94 °C ^{1}H NMR ($CDCl_3$): 1.40 (t, 3H, J=7.0 Hz); 1.92 (s, 3H); 4.23 (q, 2H, J=7.0 Hz); 9.0 (s (br), 1H). ^{13}C ($CDCl_3$, D1 set at 5s): 8.2; 14.9; 64.6; 82.2 (br); 107.1; 161.2 (br). HRMS: calcd for $C_6H_9IN_2O$+ H: 252.9838. Exptl: 252.9803.

2.16. 3-Ethoxy-5-iodo-4-phenyl-1*H*-pyrazole (4d)

Compound **3d** (1.33 g, 0.0070 mol) *N*-iodosuccinimide (1.67 g, 0.0074 mmol) were refluxed in dichloroethane (50 mL) under an inert atmosphere for 2 h. This was diluted with ethyl acetate, washed with a solution of sodium sulfite, with brine, dried over magnesium sulfate and concentrated to dryness. The residue was purified by a chromatography over silica gel (cyclohexane/ethyl acetate 4/1) to yield compound **4d** (1.47 g, 66%). Further elution led to the isolation of unreacted compound **3d** (0.19 g, 14%). Mp 144 °C ^{1}H NMR ($CDCl_3$): 1.44 (t, 3H, J=7.0 Hz); 4.32 (q, 2H, J=7.0 Hz); 7.32 (m, 1H); 7.43 (m, 2H); 7.61; (m, 2H); 9.50 (s (br), 1H). ^{13}C ($CDCl_3$; D1 set at 5s): 14.8; 65.0; 80.9 (br); 111.6; 127.0; 128.2; 128.8; 130.7; 159.9. HRMS: calcd for $C_{11}H_{11}IN_2O$+ H: 314.9994. Exptl: 314.9970.

2.17. 4,5-Diiodo-3-ethoxy-1*H*-pyrazole (4e)

3-Ethoxy-1*H*-pyrazole (**1a**) (3.48 g, 0.031 mol) *N*-iodosuccinimide (14.66 g, 0.065 mol) were refluxed in dichloroethane (80 mL) under an inert atmosphere for 11h. This was diluted with ethyl acetate, washed with a solution of sodium sulfite, with brine, dried over magnesium sulfate and concentrated to dryness. The residue was purified by a chromatography over silica gel (cyclohexane/ethyl acetate 4/1) to yield compound **4e** as a slightly yellow powder (9.69 g, 85%). A similar procedure, from compound **3e**, with 1.1 equiv of NIS led to compound **4e** in a similar yield; mp 108 °C ^{1}H NMR ($CDCl_3$): 1.42 (t, 3H, J=7.0 Hz); 4.28 (q, 2H, J=7.0 Hz); 9.65 (s (br), 1H). ^{13}C NMR ($CDCl_3$): 14.7; 59.2; 65.7; 91.7; 136.6. HRMS: calcd for $C_5H_6I_2N_2$+H: 364.8648; Found: 364.8649.

2.18. Iodination of 3f–j, preparation of compounds 4f–j

The considered 3-trifluoromethylpyrazole (9.6 mmol) and *N*-iodosuccinimide (2.38 g, 10 mmol) in dichloroethane (14 mL) were heated in a microwave oven as described for each case. The resulting mixture was diluted with ethyl acetate and decolorized with a solution of sodium disulfite. The organic layer was washed with brine five times, dried over magnesium sulfate and concentrated to dryness. The residue was further purified as described below.

*2.18.1. Ethyl 3-iodo-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate (**4f**).* The reaction was heated in a microwave oven for 1 h and a half at 190 °C. The residue was purified by a chromatography over silica gel (cyclohexane/ethyl acetate 3/1) to yield compound **4f** as a white powder (1.81 g, 56%); mp 119 °C ^{1}H NMR ($CDCl_3$): 1.40 (t, 3H, J=7.0 Hz); 4.40 (q, 2H, J=7.0 Hz); 12.7 (s (br), 1H). ^{13}C NMR ($CDCl_3$; D1 set to 10 s): 14.0; 61.7; 88.7 (br); 116.0; 119.6 (q, J=268 Hz); 142.6 (br); 160.5. HRMS: calcd for $C_7H_6IF_3N_2O_2$+H: 334.9504; Found: 334.9502.

*2.18.2. 5-Iodo-4-methyl-3-(trifluoromethyl)-1H-pyrazole (**4g**).* The reaction was heated in a microwave oven 30 min at 140 °C. The residue was dispersed in boiling water (100 mL) filtered and dried in open air to yield compound **4g** as a white powder (7.2 g, 90%); mp 117 °C ^{1}H NMR ($CDCl_3$): 2.14 (s, 3H); 12.2 (s (br), 1H). ^{13}C NMR ($CDCl_3$): 9.6; 77.2; 120.6; 120.8 (q, J=272 Hz); 139.2 (br). HRMS: calcd for $C_5H_4IF_3N_2$+H: 276.9450; Found: 276.9436.

*2.18.3. 5-Iodo-4-phenyl-3-(trifluoromethyl)-1H-pyrazole (**4h**).* The reaction was heated in a microwave oven 2 h at 140 °C. The residue was purified by a chromatography over silica gel (cyclohexane/ethyl acetate 8/1) to yield compound **4h** as a white powder (2.43 g, 82%); mp 160 °C ^{1}H NMR ($CDCl_3$): 7.42 (m, 2H); 7.48 (m, 3H); 11.90 (s (br), 1H). ^{13}C NMR ($CDCl_3$): 77.2; 120.4 (q, J=267 Hz); 126.7; 128.4; 128.5; 129.7; 129.8 (br); 130.0. HRMS: calcd for $C_{10}H_6IF_3N_2$−H: 336.9450; Found: 336.9495.

*2.18.4. 4-Chloro-5-iodo-3-(trifluoromethyl)-1H-pyrazole (**4i**).* The reaction was heated in a microwave oven for 1 h at 190 °C. The residue was purified by a chromatography over silica gel (dichloromethane–ethanol from 100/0 to 98/2) to yield compound **4i** as a white powder (2.98 g, 54%) along with less pure chromatographic fractions. (Note: this compound is hardly visible on TLC, however the UV detector of the chromatography apparatus detects it fine); mp 96 °C ^{1}H NMR (DMSO-d_6): 14.5 (s (br), 1H). ^{13}C NMR (DMSO-d_6, D1 set to 10 s): 88.8; 114.3; 120.7 (q, J=267 Hz); 138.5 (q, J=37 Hz). HRMS: calcd For $C_4HClF_3IN_2$−H: 296.8904; Found: 296.8908.

*2.18.5. 4,5-Diiodo-3-(trifluoromethyl)-1H-pyrazole (**4j**).* The reaction was heated in a microwave oven for 45 min at 190 °C. The residue was purified by a chromatography over silica gel (cyclohexane/ethyl acetate 7/1) to yield compound **4j** as a white powder (5.3 g, 85%); mp 129 °C ^{1}H NMR (DMSO-d_6): 14.47 (s (br), 1H). ^{13}C NMR (DMSO-d_6, D1 set to 10 s): 70.8; 98.0; 120.5 (q, J=268 Hz); 143.7 (q, J=39 Hz). HRMS: calcd for $C_4HF_3I_2N_2$+H: 388.8260; Found: 388.8258.

*2.18.6. 3-Ethoxy-4-methyl-1H-pyrazole-5-carboxylic acid (**5**).* Ethyl 3-ethoxy-4-methyl-1*H*-pyrazole-5-carboxylate[31](3.6 g, 0.018 mol) and sodium hydroxide (1.5 g, 0.036 mol) were refluxed in water (40 mL) for 45 min. The solution was cooled and made acid with 2 N hydrochloric acid. The resulting precipitate was filtered, washed with water and dried under vacuum at 65 °C to yield compound **5** as a white solid (2.8 g, 93%); mp 194 °C ^{1}H NMR (DMSO-d_6): 1.30 (t, 3H, J=7.0 Hz); 2.02 (s, 3H); 4.16 (q, 2H, J=7.0 Hz); 12.4 (s (br), 1H); 13.1 (s (br), 1H). ^{13}C (DMSO-d_6; D1 set at 5s): 7.3; 15.2; 64.5; 103.7; 131.7; 161.5; 161.6. HRMS: calcd for $C_7H_{10}N_2O_3$+H: 171.0770. Exptl: 171.0770.

2.19. Ethyl 1-(4-chloro-4-(ethoxycarbonyl)-5-oxo-4,5-dihydro-1*H*-pyrazol-3-yl)-3-ethoxy-1*H*-pyrazole-4-carboxylate (7)

Pyrazole **3a** (3 g, 0.0162 mol) and *N*-chlorosuccinimide (2.4 g, 0.0179 mol) were heated in dichloroethane (14 mL) using a microwave oven at 130 °C for 40 min. The resulting solution was concentrated to dryness and purified by a chromatography over silica gel (cyclohexane/ethyl acetate 4/1). The main fraction collected (1.21 g) was further purified by a recrystallisation in a mixture of toluene and cyclohexane to yield compound **7** as an off-white solid (0.7 g, 23%); mp 129 °C ^{1}H NMR (DMSO-d_6): 1.24 (t, 3H, J=7.0 Hz); 1.28 (t, 3H, J=7.0 Hz); 1.32 (t, 3H, J=7.0 Hz); 4.33 (m, 6H); 8.68 (s, 1H); 12.40 (s (exch.), 1H). ^{13}C NMR (DMSO-d_6): 14.2; 14.6 (two signals); 60.6; 61.0 (C4); 64.7; 65.9; 104.8 (C4′); 133.5 (CH-5′); 147.6 (C3); 160.7; 160.8; 162.6; 167.4 (C5). HRMS: calcd for $C_{14}H_{17}Cl^{35}N_4O_6$+H: 373.0915; Found: 373.0891.

2.20. Preparation of compounds 8 and 9

Pyrazole **3a** (2.23 g, 0.0121 mol) and *N*-chlorosuccinimide (1.7 g, 0.0127 mol) were dissolved in dichloroethane (10 mL) and stirred at 20 °C for 24 h. The resulting solution was diluted in ethyl acetate, washed with a sodium sulfite solution, water, brine, dried over magnesium sulfate and concentrated to dryness. The not fully reduced resulting residue (2.38 g) was then boiled for 10 min in a 1/2 mixture of water and THF (100 mL) containing sodium sulfite (2 g). This was diluted in ethyl acetate and water, the organic layer was washed with water, brine, dried over magnesium sulfate and concentrated to dryness. The resulting residue was purified by a chromatography over silica gel (cyclohexane/ethyl acetate 2/1 to 0/1). The main fraction collected (0.38 g) was further purified by a recrystallisation in a mixture of toluene and cyclohexane to yield compound **8** (0.2 g, 9%). The aqueous layer of the last extraction was made acid with 2 N hydrochloric acid, extracted with ethyl acetate, the organic layer was washed with water, brine, dried over magnesium sulfate and concentrated to dryness. The resulting residue (0.37 g) was recrystallized in toluene to yield compound **9** (0.22 g, 10%).

*2.20.1. Diethyl 3,5′-diethoxy-2′H-1,3′-bipyrazole-4,4′-dicarboxylate (**8**).* Pale yellow solid, mp 153 °C ^{1}H NMR ($CDCl_3$): 1.36 (m, 6H); 1.44 (m, 6H); 9.18 (s(br), 1H); 10.2 (s(br), 1H). ^{13}C NMR ($CDCl_3$; D1 set at 6s): 14.1; 14.3; 14.4; 14.6; 60.3; 60.6; 65.2 (br); 65.8; 88.7; 103.4; 137.3; 140.4 (br); 161.7; 162.1 (br); 162.2; 163.0. HRMS: calcd for $C_{16}H_{22}N_4O_6$+H: 367.1618; Found: 367.1640.

*2.20.2. Ethyl 3-ethoxy-1-(4-(ethoxycarbonyl)-5-oxo-2,5-dihydro-1H-pyrazol-3-yl)-1H-pyrazole-4-carboxylate (**9**).* White solid, mp 159 °C ^{1}H NMR (DMSO-d_6): 1.12 (t, 3H, J=7.0 Hz); 1.25 (t, 3H, J=7.0 Hz); 1.34 (t, 3H, J=7.0 Hz); 4.08 (q, 2H, J=7.0 Hz); 4.20 (m, 4H); 8.37 (s, 1H); 11.80 (s (br), 1H); 12.80 (s (br), 1H). ^{13}C (DMSO-d_6; D1 set at 10s): 14.4; 14.7; 14.9; 59.7; 59.8; 65.1 89.7; 100.7; 138.0; 145.3 (br); 156.8 (br); 161.8 (two signals); 161.83. HRMS: calcd for $C_{14}H_{18}N_4O_6$+H: 339.1305; Found: 339.1283.

2.21. Reduction of 4e into 10 by treatment with hydrochloric acid

In a flask equipped with a condenser, compound **4e** (0.63 g, 0.0017 mol) was boiled in 2 N hydrochloric acid (20 mL) for 11 h. Extensive sublimation into the condenser of iodine or iodinemonochloride was observed. This was cooled, the solution was cautiously made basic with solid potassium carbonate and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and concentrated to dryness to yield an oil (0.37 g). Analysis (NMR and LC/MS) of this oil showed beyond any doubt that it contained a 38:62 proportion of compound **4e** and **10**. From compound **2a**, under similar condition although only after 90 min, the occurrence of 95% of the reduced compound **1a** was noted.

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