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## Introduction

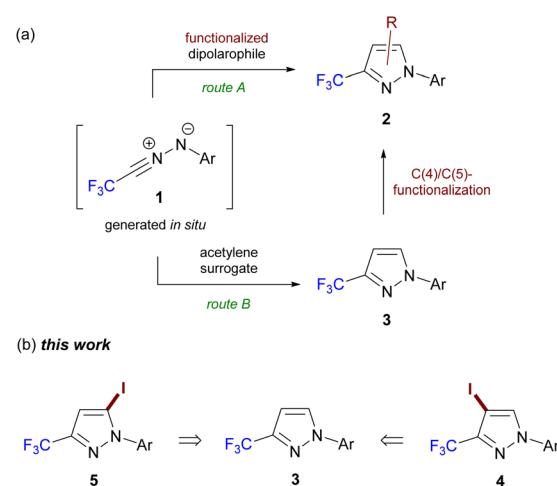
During the last decades, fluoromethylated pyrazoles have been recognized as privileged structural motifs for agrochemicals, pharmaceuticals and organic materials; therefore, they are highly attractive targets for organic synthesis.<sup>1</sup> Among the variety of protocols for the preparation of fluoromethylated pyrazoles reported thus far,<sup>1,2</sup> (3 + 2)-cycloaddition reactions of  $\text{CHF}_2$ - and  $\text{CF}_3$ -functionalized nitrile imines, formally derived from di- and tri-fluoroacetaldehyde, respectively, are highly efficient methods.<sup>3</sup> For example, electron-rich dipolarophiles such as enol ethers and arynes<sup>4a,b</sup> as well as electron-deficient olefins, *e.g.* nitro- and cyano-alkenes,<sup>4c-f</sup> enones,<sup>4g,h</sup> and mal-imides<sup>4i</sup> are suitable agents to trap *in situ* generated nitrile imine **1**, leading to functionalized pyrazoles and the related fused systems. The approach presented in Scheme 1a (route A) is documented in the literature and offers straightforward access to target materials **2** of various substitution patterns; however, it requires access to a library of properly functionalized reactive dipolarophiles. Moreover, there are limitations to obtain regioselectivity for the reactions of **1** with non-activated ethylenes and some acetylene derivatives.<sup>5</sup> An alternative route towards C(4)-/C(5)-functionalized 3- $\text{CF}_3$ -pyrazole **3** with nitrile imine **1** as a key substrate *via* post-cyclizative functionalization of the pyrazole ring in **3** (Scheme 1, route B) has not been thoroughly explored.<sup>6</sup> Hence, the development of general protocols for the selective introduction of iodine at C(4) and C(5) in 1-aryl-3- $\text{CF}_3$ -pyrazole **3** is of interest considering the well-known utility of (hetero)aryl iodides in the synthesis of

more complex systems available through cross-coupling reactions.<sup>7</sup>

In continuation of our study on fluorinated azoles,<sup>8</sup> herein, we reported on the efficient functionalization of 1-aryl-3- $\text{CF}_3$ -pyrazole **3** to produce 4-iodo and 5-iodo-analogues **4** and **5** in a highly selective fashion (Scheme 1b). Exemplary Suzuki-Miyaura and Sonogashira coupling reactions of model C(4)-/C(5)-iodides are also presented.

## Results and discussion

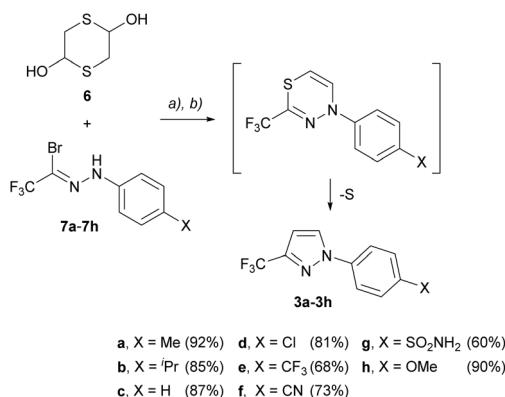
The key intermediate **3** is easily obtained by trapping *in situ* generated nitrile imine **1** with suitable acetylene equivalents.



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**Scheme 2** One-pot synthesis of 1-aryl-3-CF<sub>3</sub>-pyrazoles **3a–3h** starting with dimeric mercaptoacetaldehyde **6** and nitrile imine precursors **7a–7h**: (a) Et<sub>3</sub>N, DCM, 4 h, rt; (b) pTsCl, 16 h.

For example, we previously disclosed a one-pot protocol based on (3 + 3)-cycloaddition of 1,3-dipole **1** with mercaptoacetaldehyde, followed by spontaneous Eschenmoser ring-contraction of the first formed 1,3,4-thiadiazine.<sup>9a</sup> More recently, the Hu group disclosed an alternative method with (2-bromoethyl)-diphenylsulfonium triflate applied as an acetylene surrogate.<sup>9b</sup> As shown in Scheme 2, we commenced our study with 1-aryl-3-CF<sub>3</sub>-pyrazole **3** prepared following the former general protocol. Starting with dimeric mercaptoacetaldehyde (1,4-dithiane-2,5-diol, **6**) and hydrazonoyl bromides **7a–7h** as nitrile imine precursors, a series of eight compounds **3a–3h** bearing selected *para*-substituted phenyl substituents at N(1) (X = Me, <sup>i</sup>Pr, H, Cl, CF<sub>3</sub>, CN, SO<sub>2</sub>NH<sub>2</sub> and OMe) was prepared in 60–92% yield.

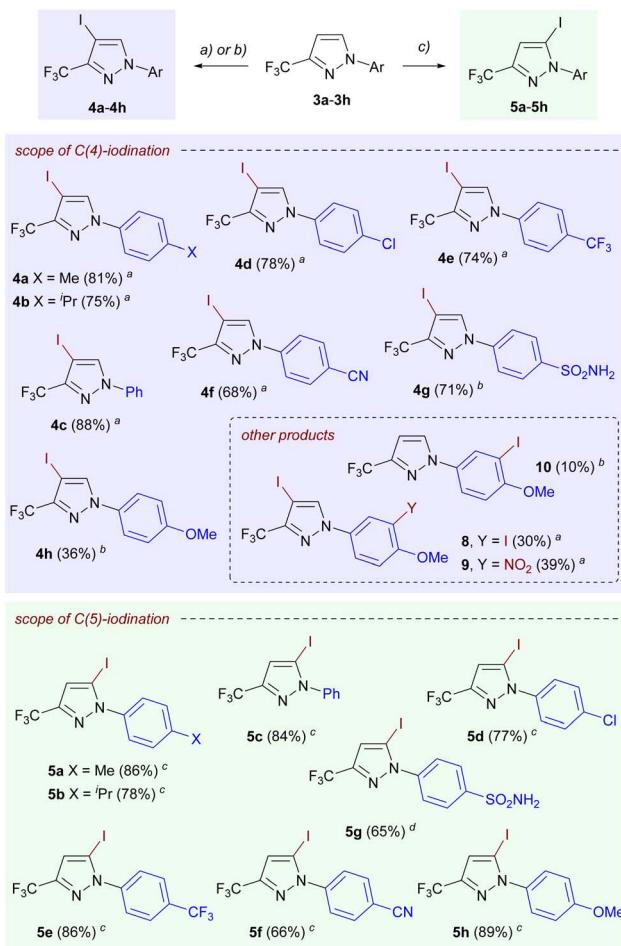
The general methods for direct iodination of structurally diverse pyrazoles usually comprise the use of elemental iodine under oxidative conditions.<sup>10</sup> Also, the applications of common inorganic salts such as NaI and KI-KIO<sub>3</sub>, as well as organic iodocompounds including NIS, Me<sub>4</sub>NI, 1,3-diiodo-5,5-dimethylhydantoin (DIH), and aryliodine(III) diacetates as iodine sources are known.<sup>11</sup> More recently, Peglow and Nascimento reported an elegant one-pot protocol using potassium iodate (KIO<sub>3</sub>) and diphenyl diselenide (PhSe)<sub>2</sub> as catalysts for the selective iodination of *in situ* generated pyrazoles under acidic conditions.<sup>11g</sup> Despite remarkable progress in iodination reactions of classical *N*-alkyl- and *N*-aryl-pyrazoles, synthetic methods towards fluoromethylated iodopyrazole derivatives are only reported to a limited extent.<sup>12</sup>

In the first part of this study, we followed the work by Rodríguez-Franco on the regioselective iodination of pyrazoles using I<sub>2</sub> in the presence of ceric ammonium nitrate (CAN) as mild oxidant.<sup>10b</sup> The first experiment with model compound **3a** (1.0 mmol) was conducted using a slight excess of I<sub>2</sub> (0.6 mmol) and CAN (0.6 mmol) in MeCN. Trace conversion of **3a** was observed after 24 h at room temperature, while increasing the temperature (reflux) and using an excess of iodinating agents (iodine: 1.3 equiv.; CAN: 1.1 equiv.) enabled complete consumption of the starting pyrazole in a reasonable reaction

time (overnight) (Scheme 3).<sup>‡</sup> Analysis of the crude mixture by <sup>1</sup>H NMR spectroscopy indicated the formation of a single product, and the presence of the diagnostic singlet absorption at  $\delta$  = 7.97 attributed to C(5)-H suggested the exclusive introduction of iodine at C(4) of the pyrazole ring. After standard aqueous workup followed by simple filtration through a short chromatography column (FCC), the expected product **4a** was isolated in 81% yield. <sup>13</sup>C and <sup>19</sup>F NMR analyses of the obtained material supplemented by MS measurements and combustion analysis confirmed the structure of **4a** as the desired 4-iodo-1-tolyl-3-trifluoromethylpyrazole and its analytical purity. In <sup>13</sup>C NMR spectra, the expected remarkable high-field shift ( $\Delta \approx 50$ ) is noteworthy for the signal attributed to C(4) from  $\delta$  = 105.9 (q, <sup>3</sup>J<sub>C-F</sub> ≈ 2.2 Hz) in **3a** to  $\delta$  = 55.7 (q, <sup>3</sup>J<sub>C-F</sub> ≈ 1.6 Hz) in **4a**.

<sup>‡</sup> General procedure A for the synthesis of 4-iodopyrazoles **4a–4f**: A solution of 1-aryl-3-trifluoromethylpyrazole **3** (1.0 mmol), CAN (603 mg, 1.1 mmol), and elemental iodine (330 mg, 1.3 mmol) in MeCN (6 mL) was refluxed overnight. After the solvent was removed *in vacuo*, the residue was dissolved in DCM (15 mL), the mixture was washed with sat. aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (5 mL), then with water (10 mL), and the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was evaporated and the crude product **4** was purified by filtration through a short silica gel pad (FCC) or by standard column chromatography (CC). 4-Iodo-1-(*p*-tolyl)-3-trifluoromethyl-1*H*-pyrazole (**4a**): FCC (SiO<sub>2</sub>, hexane/DCM 3:2); yellow oil, 285 mg (81%). <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)  $\delta$  2.42 (s, 3H), 7.29–7.31 (m, 2H), 7.53–7.55 (m, 2H), 7.97 (s, 1H, 5-H). <sup>13</sup>C{<sup>1</sup>H} NMR (151 MHz, CDCl<sub>3</sub>)  $\delta$  21.1, 55.9 (q, <sup>3</sup>J<sub>C-F</sub> ≈ 1.6 Hz), 119.7, 121.0 (q, <sup>1</sup>J<sub>C-F</sub> = 270.2 Hz), 130.3, 134.4, 136.7, 138.5, 144.9 (q, <sup>2</sup>J<sub>C-F</sub> = 37.2 Hz). <sup>19</sup>F NMR (565 MHz, CDCl<sub>3</sub>):  $\delta$  –61.72 (s, CF<sub>3</sub>). IR (neat)  $\nu$  1521, 1470, 1394, 1230, 1163, 1129, 1066, 992, 813 cm<sup>–1</sup>. ESI-MS (*m/z*): 353.1 (100, [M + H]<sup>+</sup>). Anal. calcd. for C<sub>11</sub>H<sub>8</sub>F<sub>3</sub>IN<sub>2</sub> (352.1): C 37.52, H 2.29, N 7.96; found: C 37.45, H 2.33, N 7.85. General Procedure B for the synthesis of 4-iodopyrazoles **4g** and **4h**: To a solution of pyrazole **3** (1.0 mmol) in glacial acetic acid (1 mL) was added a solution of NIS (338 mg, 1.5 mmol) in TFA (1 mL) and the resulting mixture was heated overnight at 80 °C. The solution was cooled to room temperature, diluted with DCM (60 mL), washed with sat. aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (2  $\times$  5 mL), and then with sat. aq. NaHCO<sub>3</sub> (3  $\times$  5 mL). The organic layer was separated, dried over Na<sub>2</sub>SO<sub>4</sub>, and solvents were removed *in vacuo*. The products were purified by column chromatography. 4-(4-Iodo-3-trifluoromethyl-pyrazol-1-yl)-benzenosulfonamide (**4g**): CC (SiO<sub>2</sub>, hexane/EtOAc 2:3); light yellow solid, 296 mg (71%); mp 166–168 °C. <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  7.48 (s<sub>br</sub>, 2H, NH<sub>2</sub>), 7.97–7.99 (m, 2H), 8.05–8.08 (m, 2H), 9.05 (s, 1H, 5-H). <sup>13</sup>C{<sup>1</sup>H} NMR (151 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  59.7 (br), 119.4, 120.9 (q, <sup>1</sup>J<sub>C-F</sub> = 270.0 Hz), 127.4, 136.7, 140.2, 143.2, 144.1 (q, <sup>2</sup>J<sub>C-F</sub> = 36.4 Hz). <sup>19</sup>F NMR (565 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  –60.72 (s, CF<sub>3</sub>). IR (neat)  $\nu$  3340, 3247, 1592, 1477, 1387, 1331, 1234, 1156, 1118, 1096, 992, 910, 835 cm<sup>–1</sup>. HRMS ((–)ESI-TOF) *m/z*: [M–H]<sup>–</sup> calcd. for C<sub>10</sub>H<sub>7</sub>F<sub>3</sub>IN<sub>3</sub>O<sub>2</sub>S 415.9177, found 415.9178. General Procedure C for the synthesis of 5-iodopyrazoles **5a–5h**: To a solution of 1-aryl-3-CF<sub>3</sub>-pyrazole **3** (1.0 mmol) in dry THF (5 mL) was added *n*-BuLi (2.5 M in hexane, 0.52 mL, 1.3 mmol) dropwise under vigorous stirring at –78 °C. After 10 min, a solution of iodine (356 mg, 1.4 mmol) in dry THF (3 mL) was added and the mixture was allowed to reach room temperature within 4 h. The resulting was diluted with DCM (30 mL), washed with sat. aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (10 mL), then with water (5 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and the solvents were removed under reduced pressure. Crude product was isolated by filtration through a short silica gel pad (FCC). 5-Iodo-1-(*p*-tolyl)-3-trifluoromethyl-1*H*-pyrazole (**5a**): FCC (SiO<sub>2</sub>, hexane/DCM 1:1); light orange solid, 303 mg (86%). <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)  $\delta$  2.44 (s, 3H), 6.86 (s, 1H, 4-H), 7.30–7.31 (m, 2H), 7.38–7.40 (m, 2H). <sup>13</sup>C{<sup>1</sup>H} NMR (151 MHz, CDCl<sub>3</sub>)  $\delta$  21.3, 83.0, 115.1 (q, <sup>3</sup>J<sub>C-F</sub> ≈ 2.1 Hz), 120.8 (q, <sup>1</sup>J<sub>C-F</sub> = 269.3 Hz), 126.3, 129.7, 137.1, 139.9, 145.4 (q, <sup>2</sup>J<sub>C-F</sub> = 38.8 Hz). <sup>19</sup>F NMR (565 MHz, CDCl<sub>3</sub>):  $\delta$  –62.39 (s, CF<sub>3</sub>). IR (neat)  $\nu$  1506, 1457, 1368, 1230, 1167, 1118, 1085, 980, 965, 824, 801 cm<sup>–1</sup>. ESI-MS (*m/z*): 353.1 (100, [M + H]<sup>+</sup>). Anal. calcd. for C<sub>11</sub>H<sub>8</sub>F<sub>3</sub>IN<sub>2</sub> (352.1): C 37.52, H 2.29, N 7.96; found: C 37.62, H 2.31, N 7.77.

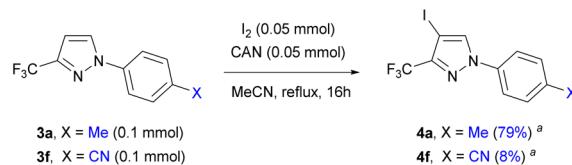




**Scheme 3** Synthesis of 4- and 5-iodopyrazoles 4 and 5: (a)  $I_2$  (1.3 equiv.), CAN (1.1 equiv.), MeCN, reflux, 16 h; (b) NIS (1.5 equiv.), AcOH/TFA (1:1), 85 °C, 16 h; (c)  $n$ -BuLi (1.3 equiv.), -78 °C, THF, 10 min, then  $I_2$  (1.4 equiv.), -78 °C to rt, 4 h; (d)  $n$ -BuLi (3.0 equiv.), THF/TMEDA, -78 °C, 10 min, then  $I_2$  (3.2 equiv.), -78 °C to rt, 4 h.

With the established reaction conditions, the  $i$ -Pr-functionalized derivative **3b** was examined to afford the expected **4b** as the sole material, which was isolated by FCC in 75% yield (Scheme 3). In this case, there was no competitive iodination of the benzylic-like position in the  $i$ -Pr group or the *N*-aromatic substituent. Notably, the reaction proceeded smoothly even in the case of substrates bearing electron-deficient *N*-aryl substituents (**3d**–**3f**), although the introduction of strong electron-withdrawing groups X such as  $CF_3$  and CN in **3e** and **3f**, respectively, decreased the reaction rate according to TLC. In addition, a competition experiment was conducted wherein a mixture of equimolar amounts of **3a** (0.1 mmol) and **3f** (0.1 mmol) was treated with a deficient amount of iodine source ( $I_2$ /CAN; 0.05 mmol each) to produce a mixture of products **4a** and **4f** in a *ca.* 10 : 1 ratio after overnight heating (Scheme 4).

In contrast, the attempted iodination of sulfonamide-functionalized pyrazole **3g** under the applied conditions led to a complex mixture in which no desired 4-iodopyrazole **4g** was detected. On the other hand, treatment of **3h** ( $X = OMe$ ) with CAN/ $I_2$  resulted in simultaneous iodination of the *p*-anisyl

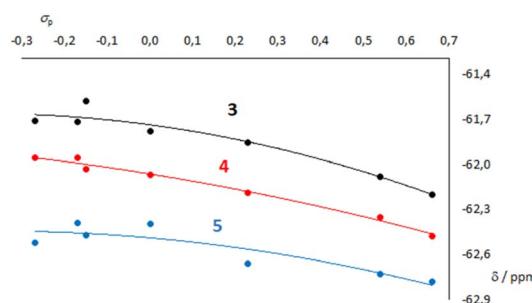


**Scheme 4** Competition experiment between **3a** and **3f**: <sup>a</sup> conversion of individual starting materials based on <sup>1</sup>H NMR of the reaction mixture.

group to afford pyrazole **8** (30% yield), a minor component of the mixture, along with nitro analogue **9** (39% yield), isolated as the major product. The experiment revealed lesser-known nitrating activity of ceric ammonium nitrate in MeCN solutions, which is in accordance to previous reports on CAN-mediated *ortho*-selective nitration of some electron-rich arenes.<sup>13</sup> Hence, the reaction was conducted under acidic conditions using a 1 : 1 mixture of glacial acetic acid and TFA as reaction media and employing *N*-iodosuccinimide (NIS) as a source of iodide to suppress the nucleophilicity of functional groups in **3g** and **3h**.<sup>12b</sup> In this case, the desired sulphonamide-functionalized product **4g** was obtained in 71% yield. However, in the case of **3h**, the expected product **4h** (36% yield) was obtained along with small amounts of another moniodinated product, 1-(3-iodo-4-methoxyphenyl)-3-trifluoro-methylpyrazole (**10**, 10%), formed *via* alternative attack of electrophilic iodine onto the methoxyphenyl substituent.

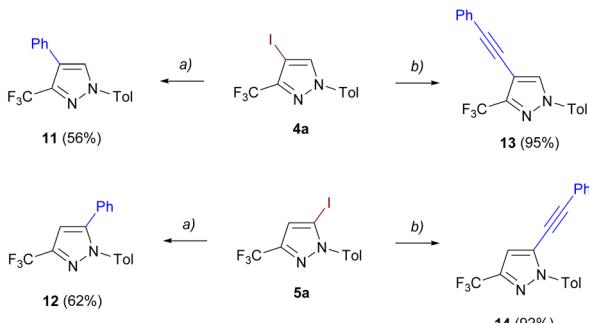
In the synthesis of a second series of iodopyrazoles of type **5**, we benefited from the remarkable acidity of the C(5)-H in starting 1-aryl-3- $CF_3$ -pyrazoles **3**.<sup>9a</sup> As shown in Scheme 3, treatment of **3a** with a slight excess of *n*-BuLi at -78 °C in dry THF smoothly generated the corresponding lithium 5-pyrazolide,<sup>14</sup> which was trapped by elemental iodine to produce the target 5-iodo derivative **5a** (86% yield) after standard aqueous workup. Following the devised protocol,<sup>‡</sup> a set of isomeric iodides **5b**–**5h** was obtained in 65–89% yield. Notably, threefold excess *n*-BuLi in the presence of TMEDA as the co-solvent enabled the efficient iodination of sulphonamide **3g** (65% yield).<sup>9a</sup>

The spectroscopic properties of iodides **4** and **5** also deserve a brief comment. Increasing the electron-withdrawing character of substituent X in starting pyrazoles **3** increases shielding of <sup>19</sup>F nuclei (Fig. 1). Analysis of chemical shifts demonstrate that they non-linearly correlate with the Hammett



**Fig. 1** Correlation of <sup>19</sup>F chemical shifts for a series of pyrazoles **3**–**5**.





**Scheme 5** Selected cross-coupling reactions of isomeric iodides **4a** and **5a**: (a) phenylboronic acid (1.3 equiv.),  $\text{Pd}(\text{PPh}_3)_4$  (30 mol%),  $\text{K}_2\text{CO}_3$ ,  $\text{THF}/\text{H}_2\text{O}$ , reflux, 2 d; (b) phenylacetylene (1.25 equiv.),  $\text{Pd}(\text{PPh}_3)_4$  (10 mol%),  $\text{CuI}$  (10 mol%),  $\text{THF}/\text{Et}_3\text{N}$ , 80 °C, 24 h.

$\sigma_p$  parameter.<sup>15</sup> The introduction of iodine at C(4) and C(5) of the pyrazole ring (in **4** and **5**, respectively) results in further up-field shift, although slightly stronger shielding is caused by the latter functionalization. The observed trends are according to so-called “normal” fluorine chemical shifts that are typical for trifluoromethylated benzene derivatives, which supplements the understanding of normal and reverse fluorine NMR chemical shifts.<sup>16</sup>

Next, compounds **4a** and **5a** were examined in model cross-coupling reactions to demonstrate practical utility of the newly synthesized iodides in the synthesis of more complex pyrazole analogues (Scheme 5). The expected 4-phenylpyrazole **11** was obtained in 56% yield following the treatment of **4a** with phenylboronic acid under classical Suzuki–Miyaura reaction conditions using  $\text{Pd}(\text{PPh}_3)_4$  as a catalyst. A similar result was observed for **5a** to afford 5-phenylated derivative **12** (62%).

Another pair of isomeric products **13** and **14** functionalized with the phenylethynyl group was prepared *via* Sonogashira coupling in >90% yield.

## Conclusions

1-Aryl-3-CF<sub>3</sub>-pyrazoles were suitable building blocks for highly selective iodination to provide access to C(4)- and C(5)-iodides. The CAN-induced reaction with elemental iodine provided products functionalized at C(4) of the pyrazole ring, while the isomeric 5-iodo products were obtained by trapping of the respective *in situ* generated lithium pyrazolide with I<sub>2</sub>. The title products are valuable reagents for the synthesis of more complex trifluoromethylated pyrazoles as exemplified by the synthesis of phenyl- and phenylethynyl-functionalized derivatives *via* Suzuki–Miyaura and Sonogashira cross-coupling reactions, respectively.

## Data availability

The data supporting this article have been included as part of the ESI.† In addition, raw NMR data (FID) as well as pdf. copies of the IR, MS and EA analyses conducted for all new compounds are available from the corresponding author.

## Author contributions

MJ and GUJ designed experiments; KŚ and GUJ synthesized and characterized the studied materials; MJ drafted the manuscript; all authors contributed to the final version of the paper.

## Conflicts of interest

There are no conflicts to declare.

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