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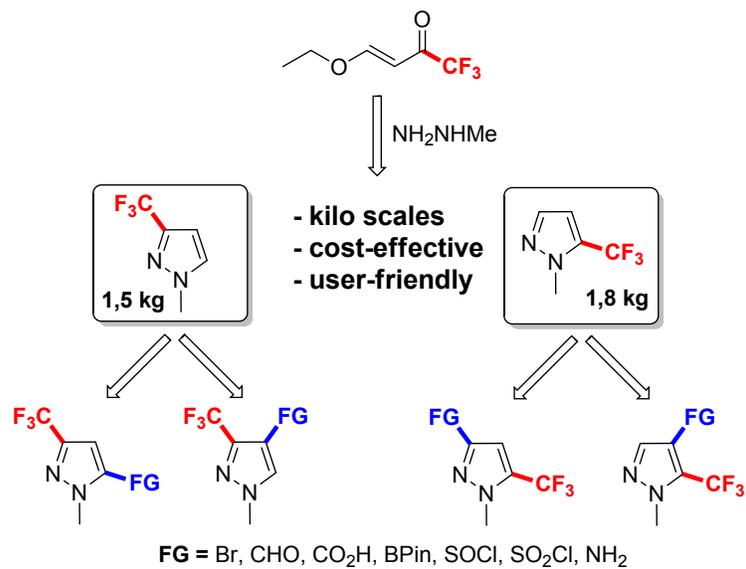
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18
19 ABSTRACT. A new, high yielding and practical synthesis of 1-methyl-3-(trifluoromethyl)-
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22 1*H*-pyrazole and 1-methyl-5-(trifluoromethyl)-1*H*-pyrazole, key intermediates for
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25 important Medicinal and Agro Chemistry relevant building blocks, is developed. One step
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28 procedure for the regioisomeric mixture of target pyrazoles was proposed starting from 4-
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31 ethoxy-1,1,1-trifluoro-3-buten-2-one. The procedure for separation of this mixture was
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33
34 elaborated on the basis of the boiling point vs. pressure diagrams analysis. The efficient
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37 synthetic strategies to regioisomeric building blocks bearing CF₃-group at the 3-rd and
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40 the 5-th positions were demonstrated. A set of 1-methyl-3-(trifluoromethyl)-1*H*-pyrazoles
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43 containing such functional group as aldehyde, acid, boron pinacolate, lithium sulfinate
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45
46 and sulfonyl chloride was synthesized based on lithiation of 1-methyl-3-(trifluoromethyl)-
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50
51 1*H*-pyrazole in flow reactor. The bromination of both 1-methyl-3-(trifluoromethyl)-1*H*-
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3 pyrazole and 1-methyl-5-(trifluoromethyl)-1*H*-pyrazole by NBS in mild conditions was
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7 performed. The introduction of the functional group into the 4-th position of 1-methyl-5-
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10 (trifluoromethyl)-1*H*-pyrazole was illustrated by the optimized synthesis of the
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13
14 corresponding aldehyde and acid based on Br-Li exchange in the appropriate bromide.
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16
17 Alternatively, the introduction of the functional group (acid and boron pinacolate) into the
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20 5-th position of 1-methyl-5-(trifluoromethyl)-1*H*-pyrazole was performed based on DoM
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23
24 reaction of 4-bromo-1-methyl-5-(trifluoromethyl)pyrazole followed by catalytic reductive
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28 debromination.
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33 KEYWORDS. trifluoromethyl pyrazoles, regioisomer separation, flow lithiation, bromine-
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36 lithium exchange, direct *ortho*-methylation, hydrogenative dehalogenation; building
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40 blocks.
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43 INTRODUCTION

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46 Pyrazole derivatives are the scaffolds of primary importance for medicinal,^{1,2}
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49 agricultural,³ supramolecular⁴ chemistry as well as for materials sciences.^{5,6}
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54 3/5-Trifluoromethylpyrazoles, well-known examples of pyrazole derivatives, are key
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3 privileged fragments, which are present in many agrochemicals and pharmaceuticals.^{7,8}

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7 Among agrochemicals, herbicide Fluazolate (JV-485) I, used on winter wheat developed

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10 by Monsanto and Bayer AG, and fungicide Penthiopyrad II, developed by Mitsui

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13 Chemicals and DuPont, can be mentioned. Promising drug candidates ERDRP-00519 III,

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16 non-nucleoside inhibitor of the measles virus RNA-dependent RNA-polymerase,⁹ and

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19 compound IV, interleukin-1 receptor-associated kinase inhibitor¹⁰ can be highlighted

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22 (Figure 1). All these data clearly show that 3/5-trifluoromethylpyrazole fragments are

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25 playing an important role in different Agro and Medicinal Chemistry programs. Therefore,

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28 to continue our in-house program directed to the design and synthesis of fluorine-

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31 containing building blocks,¹¹ we desired to expand our stock by diverse functionalized

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34 3/5-trifluoromethyl pyrazoles. Among innumerable possible variations of compounds with

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37 such core, the parent N-methyl-3/5-trifluoromethyl pyrazoles bearing the functional

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40 groups at the 4-th or the 3-d/5-th positions were chosen. These simplest derivatives are

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43 useful candidates in compound libraries design due to compliance with the “rule-of-two”

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46 (Ro2).¹² On the other side, for the generation of any preliminary SAR the introduction of

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49 regioisomeric simplest N-methyl substituent is desired.

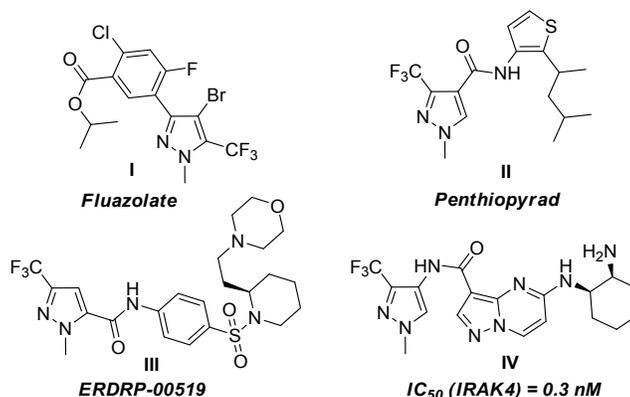
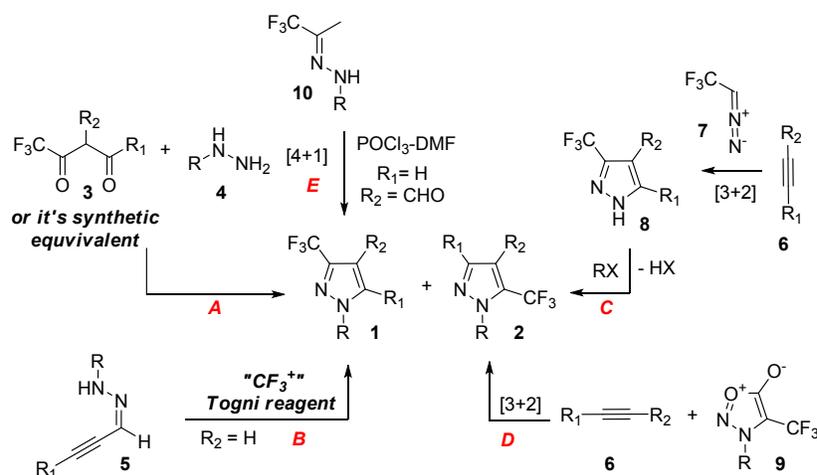


Figure 1. Examples of biologically active 1-methyl-3/5-(trifluoromethyl)-1H-pyrazoles.

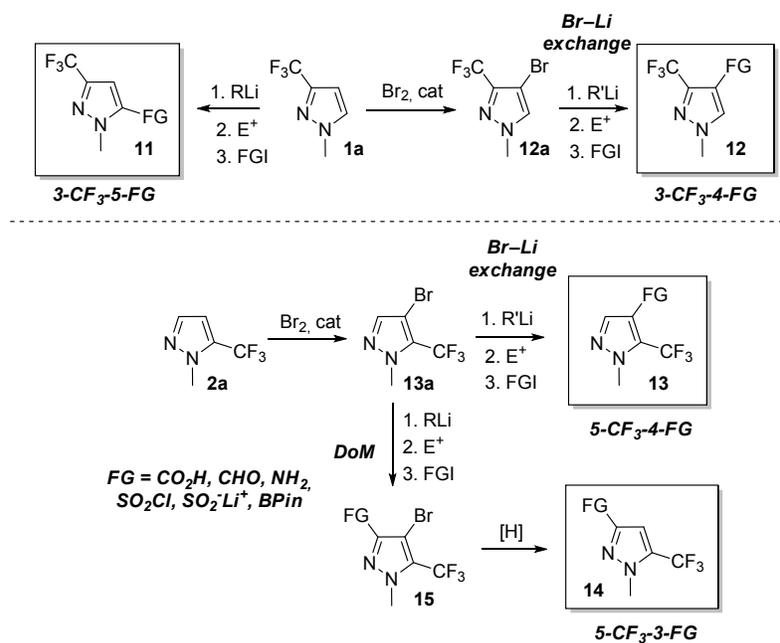
Despite the apparent simplicity, the selective synthesis of functionalized N-methyl pyrazoles is still a challenge. The traditional method for the synthesis of diverse functionalized 3/5- CF_3 -substituted pyrazoles **1** and **2** is based on the cyclocondensation of 1,3-diketones **3** (or their synthetic equivalents) with hydrazines **4** (*way A*). However, this approach is limited by the availability of prefunctionalized starting materials and poor regioselectivity. Usually it gives a mixture of hardly separable regioisomers **1** and **2**.¹³ Nevertheless, the use of acetylenic or β -functionally substituted unsaturated fluorine-containing ketones as synthetic equivalents of 1,3-diketones is more efficient. The desired pyrazoles were formed with better regioselectivity in such cases.¹⁴ All these approaches did not lead, nonetheless, to the high regioselectivity level and/or robust separation

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3 especially in the case of alkyl hydrazines. Moreover, MeNHNH₂ is the most inconvenient
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7 partner in such cyclocondensations due to the similar activity of the two nucleophilic
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10 centers. Alternatively the regioselective approach to 3-CF₃ pyrazoles **1** was developed
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13 on the basis of the electrophilic trifluoromethylation/cyclization of α,β -alkynic hydrazones
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17 **5** with Togni reagent (*way B*).¹⁵ This approach was not tested on hydrazones, derived
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20 from methylhydrazine. In addition, the cost of Togni reagent is still high for use on a large
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22
23 scale. Recently the [3+2] cycloaddition based on the reaction of alkynes **6** and *in situ*
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25
26 generated CF₃CHN₂ (**7**) affording the pyrazoles **8** was elaborated in our company (*way*
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28
29 *C*).¹⁶ This approach was later adapted to flow chemistry¹⁷ as well as for the late-stage
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31
32 functionalization.¹⁸ However, further alkylation of the *N*-unsubstituted pyrazoles **10**
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34
35 proceeds unselectively and again leads to a hardly separable mixture of regioisomers **1**
36
37
38 and **2**.¹⁹ It should be noted that the regioselective [3+2] cycloaddition involving CF₃-
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41 containing sydnone **9**, which results in 5-CF₃ pyrazoles, was reported (*way D*).²⁰ The
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44 method was applied for the synthesis of N-methyl pyrazole derivatives but the scale-up
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48 remains to be complex. To the best of our knowledge, only one example of a kilo-scale
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52 synthesis of pyrazoles, using sydnones, was described.²¹ Finally, the approach based on
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[4+1] cyclocondensation *via* Vilsmeier-Haack formylation of hydrazones derived from trifluoroacetone **10** was tested in our group (*way E*). Unfortunately, in the case of methylhydrazine derivatives, the reaction was accompanied by side processes. The synthesis of the starting hydrazone also had scale-up problems.²² The modification of the [4+1] cyclocondensation based on phthalimide-substituted acetone led to the development of the approach to (4-(trifluoromethyl)-1-methyl-1H-pyrazol-3-yl)methanamine. However, this approach was proven to be non-flexible and hazardous, because toxic SF₄ was required (Scheme 1).²³



Scheme 1. Approaches to 3/5-(trifluoromethyl)-pyrazoles.



Scheme 2. The general strategy for the synthesis of functionalized 1-methyl-3/5-(trifluoromethyl)-pyrazoles chosen for the scale-up.

In order to solve all the above-mentioned problems with regioselectivity and to elaborate the scale-up procedures, we drew our attention to seminal Schlosser paper dealing with selective lithiation of N-substituted 3/5-(trifluoromethyl)-pyrazoles.²⁴ In this work, we describe our results of optimization and scale-up the synthesis of 1-methyl-3/5-(trifluoromethyl)-pyrazoles **1a** and **2a** bearing functional groups in all possible positions. The functional groups cover the range of the commonly used ones for the array synthesis *via* amide/sulfamide coupling and reductive amination (NH₂, CO₂H, SO₂Cl, CHO)²⁵ as

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3 well as BPin derivatives and sulfinates²⁶ as partners for Pd-catalyzed cross-coupling
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7 reactions. The general strategy chosen in this work is depicted on Scheme 2. For the
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10 synthesis of the **3-CF₃-5-FG** derivatives **11**, the next sequence was studied: the lithiation
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13 at the 5-th position / electrophilic substitution / functional group interconversion of 1-
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16 methyl-3-(trifluoromethyl)-1*H*-pyrazole **1a**. For the introduction of the functional group in
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19 the 4-th position of pyrazole **1a** (the synthesis of **3-CF₃-4-FG** derivatives **12**) the
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22 electrophilic bromination/Br-Li exchange followed by functionalization was used. In the
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25 case of 5-CF₃ derivatives, the installation of function in both positions started with
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28 electrophilic bromination of **2a**. Then, in the case of **5-CF₃-4-FG** derivatives **13**, the Br-Li
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31 exchange followed by further functionalization was optimized. From the other side, for the
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34 synthesis of **5-CF₃-3-FG** building blocks **14**, the bromine atom was used as a directing
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37 group for the DoM functionalization. This atom was then removed by hydrogenation. We
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40 recently used a similar approach for the pyridine derivatives synthesis.²⁷
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49 RESULTS AND DISCUSSION

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52 The first milestone for the fulfillment of the above-mentioned strategy was to develop
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55 the kilo scale access to key starting pyrazoles **1a** and **2a**. Unfortunately, previous works,
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3 including the seminal Schlosser's paper,²⁴ in which a possible selective synthesis of both
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7 isomers of 1-methyl-5/3-(trifluoromethyl)-1*H*-pyrazoles from 4-ethoxy-1,1,1-trifluoro-3-
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10 buten-2-one **16** and MeNHNH₂ in different condition was postulated,²⁸ was not
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13 reproduced in multi-gram scale. In all cases, the mixtures of both regioisomers were
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17 formed with different ratios. Therefore, we decided to elaborate a robust protocol for their
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20 separation. Due to the low molecular weight (150 Da) we expected that the isomers could
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23 be separated by distillation.²⁹ The boiling point *vs.* pressure diagram was measured for
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27 both regioisomers. It was found, that at 1 atm the difference of the boiling points for the
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30 isomers was *ca* 50 °C (90 and 140 °C), which was very promising for the successful
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33 separation (Figure 2). The measurement of the temperature-composition diagram at 1
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36 atm for the mixture of compounds proved this assumption because, at a molar fraction of
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39 1-methyl-3-(trifluoromethyl)-pyrazole (**1a**) from 0 to *ca* 0.75 in the liquid phase, the molar
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42 fraction of 1-methyl-5-(trifluoromethyl)-pyrazole (**1b**) in the gas phase exceeded 0.95
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48 (Figure 3).
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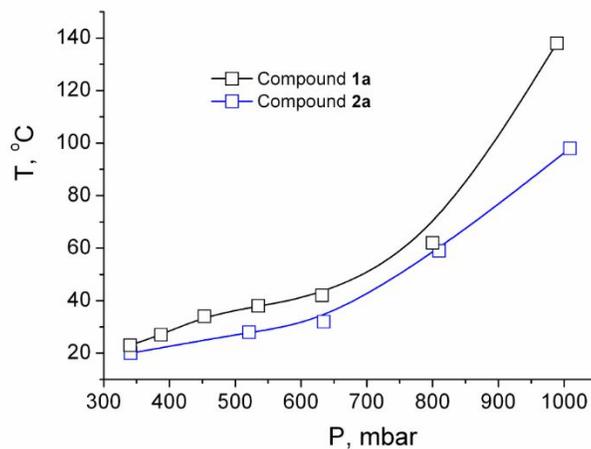


Figure 2. The boiling point–pressure diagram for compounds **1a** and **2a**.

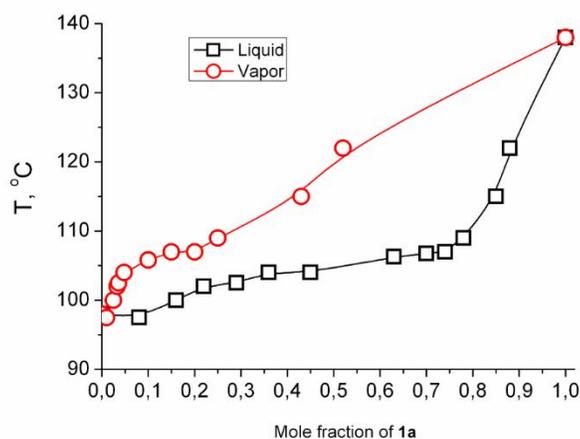
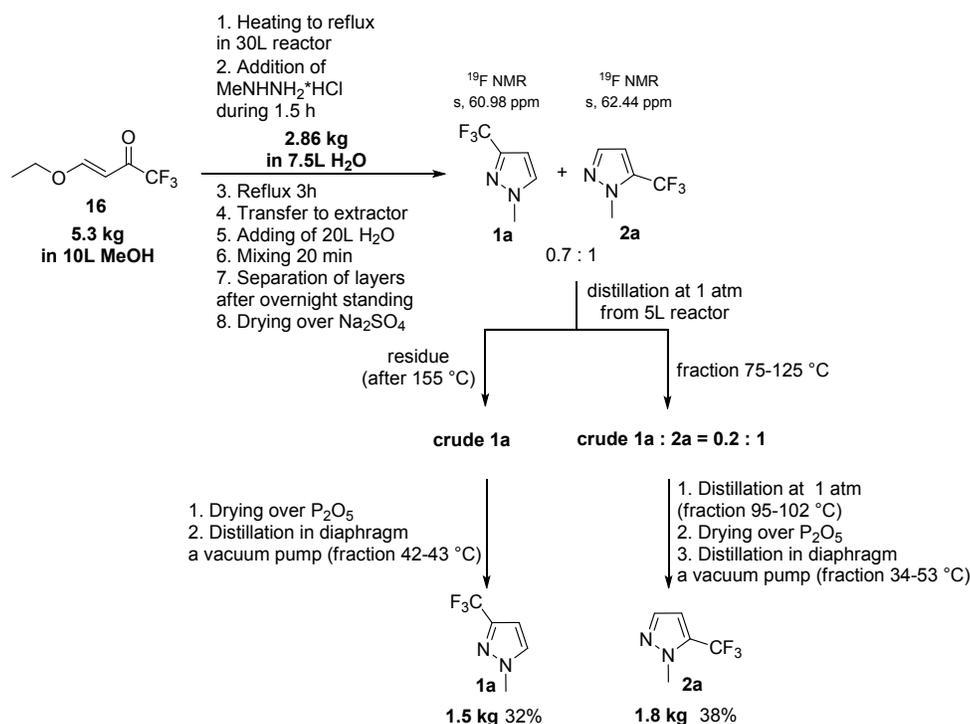


Figure 3. The temperature - composition diagram for the mixture of compounds **1a** and **2a** at 1 atm pressure.

Based on the data obtained the practical kilo scale synthesis of both individual regioisomers, including separation by distillation, was elaborated and optimized. The 4-ethoxy-1,1,1-trifluoro-3-buten-2-one reacts with MeNHNH₂ hydrochloride in the refluxed

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3 MeOH-H₂O mixture (at 1:0.75 volume ratio) affording the mixture of regioisomeric
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7 pyrazoles **1a** and **2a** in 0.7:1 ratio according to the ¹⁹F NMR spectra. The solubility of
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10 these two isomeric compounds in water is limited. Therefore, the addition of the excess
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13 of water to the reaction mixture leads to biphasic system formation, which could be easily
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16 separated. On this step, such impurities as unreacted methylhydrazine hydrochloride and
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19 HCl formed are also eliminated. The first fractional distillation of the crude mixture at 55–
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22 155 °C and atmospheric pressure gave several fractions, wherein the distillation residue
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25 contained only crude **1a**. The fraction boiling at 55–75 °C includes methanol, ethanol and
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28 a small amount of **2a**. The next fraction (75–125 °C) was the main one and contained the
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31 regioisomeric mixture of pyrazoles enriched by **2a** (0.2:1 isomers ratio). And the last
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34 fraction (125–155 °C) was the regioisomeric mixture of pyrazoles **1a** and **2a** in 1:1 ratio.
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42 The mass ratio between the main and other fractions was ca. 8:1. The further double re-
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45 distillation (the 1st at atmospheric pressure, the 2nd using diaphragm pump) of the main
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48 fraction enriched by an isomer **2a** led to the desired compound in 38% yield. It appeared
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51 to be reasonable to collect the last fraction from several synthetic runs and it also could
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54 be separated. The re-distillation of combined residues after the first distillation led to **1a**
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in 32% yield. This process worked well on 5.3 kg scale of the starting 4-ethoxy-1,1,1-trifluoro-3-buten-2-one **16** (Scheme 3).



Scheme 3. Kilogram-Scale Process for the synthesis of 1-methyl-3-(trifluoromethyl)-1*H*-pyrazole and 1-methyl-5-(trifluoromethyl)-1*H*-pyrazole.

Taking the kilo scale access to key pyrazoles **1a** and **2a**, we started the elaboration of the convenient approaches to all building blocks depicted on Scheme 4. Firstly, we tested the lithiation of 1-methyl-3-(trifluoromethyl)-1*H*-pyrazole leading to **3-CF₃-5-FG** derivatives type **12**. In order to develop the scale-up protocol, we studied the lithiation of

compound **1a** in a flow variant using our in-house developed flow systems.²⁷ In-house flow-apparatus trim is shown in Figure 4.

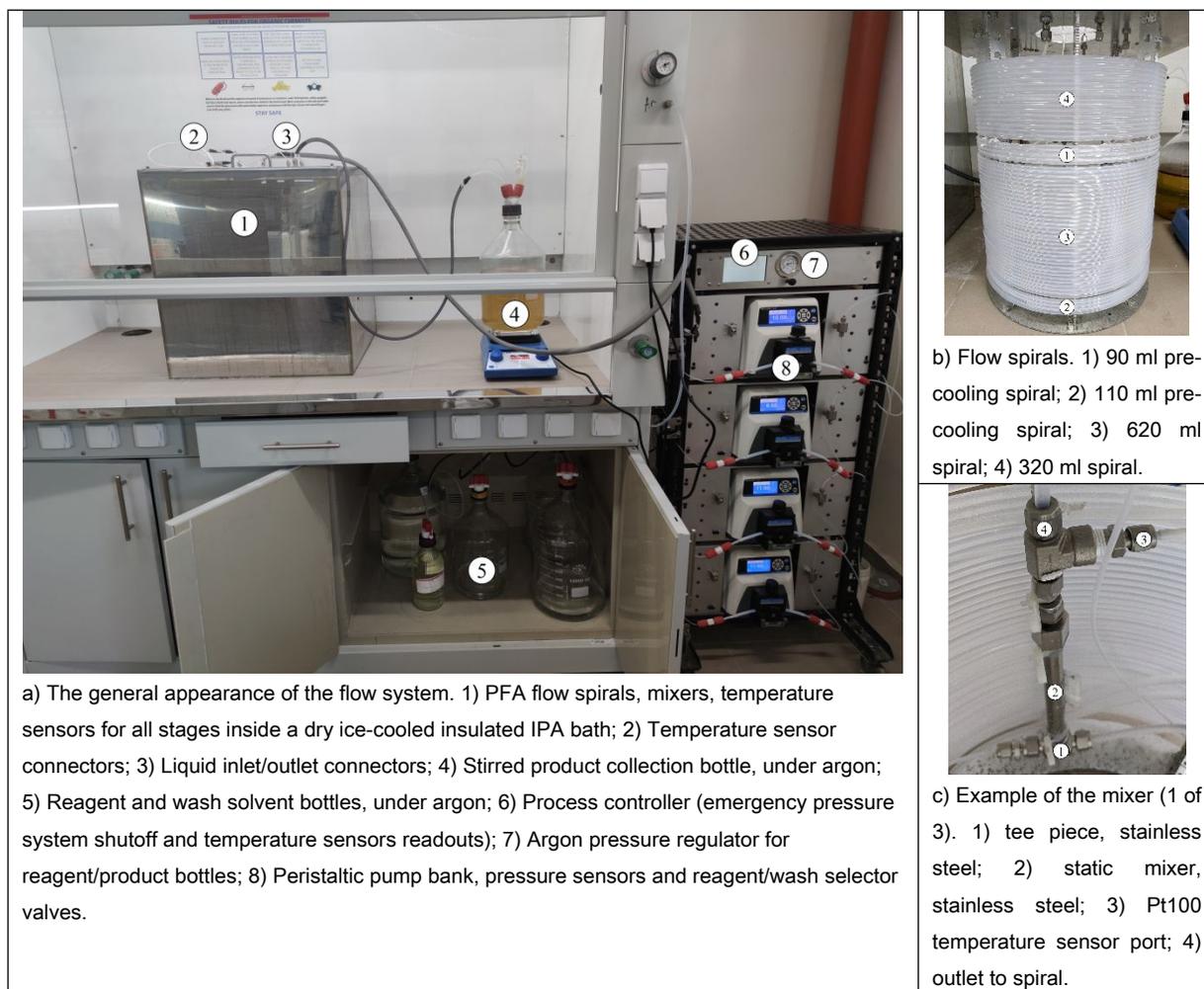
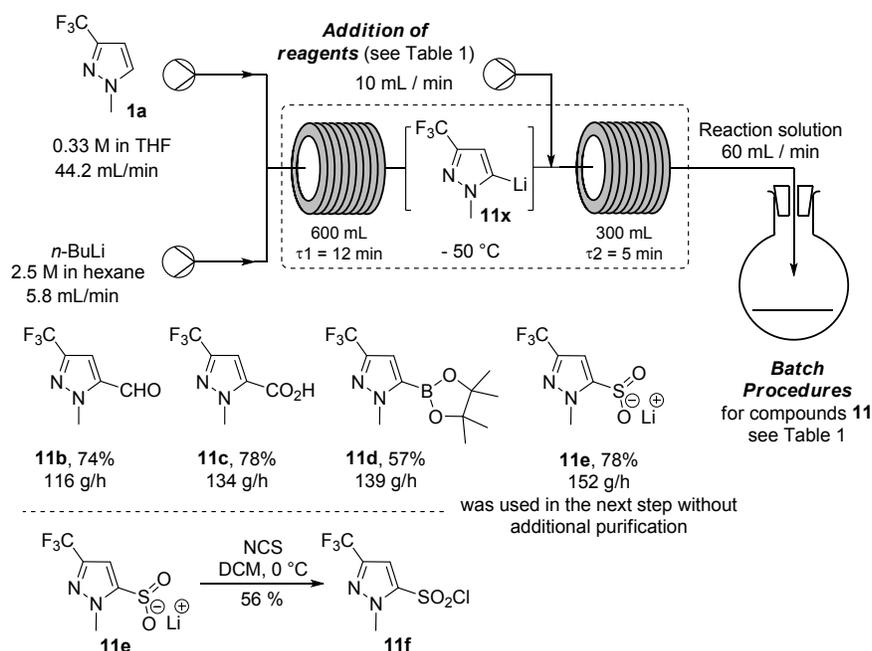


Figure 4. In-house flow-apparatus for lithiation.

The preliminary experiments with 0.33 M THF solution of pyrazole **1a** and 2.5 M solution of n-BuLi in THF allowed us to find optimal flow conditions for the generation of lithium derivative **11x** (for the general flow set up see Scheme 4, the reactor volumes were 200

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3 mL and 100 mL, respectively). More concentrated solutions of the compound **1a** in THF
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7 could not be used in our procedure due to the formation of precipitate during the flow
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10 process. It was found that the optimal temperature was $-50\text{ }^{\circ}\text{C}$ while the generation
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13 residence time was 12 min for the 600 mL reactor volume. The further treatment of the
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16 lithiated pyrazole **11x** was carried out in two different ways. In the case of synthesis of
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19 aldehyde **11b** and boronic ester derivative **11d** the solution of electrophilic reagent (1.5
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22 eq of DMF or 1.2 eq. of *t*-PrOBPin, respectively) in THF was added via the third channel
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27 and further reaction started in the second 300 mL reactor with 5 min residence time at $-$
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31 $50\text{ }^{\circ}\text{C}$. In the case of DMF, this 5 min time appeared to be sufficient for the reaction
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34 completion. The reaction mixture could be treated for further isolation/purification
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37 immediately giving the desired product **11b** in 74% yield. In the case of boronic ester
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41 derivative **11d** the reaction time 5 min at $-50\text{ }^{\circ}\text{C}$ was not sufficient for its completion.
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45 Therefore, in this case the collected reaction mixture was additionally maintained in a
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48 batch reactor at room temperature overnight before product isolation. The yield of the
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51 purified boronic ester derivative **11d** was 57%. In the case of acid **11c** and lithium
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55 pyrazolylsulfinate **11e**, the electrophilic reagents were gaseous. Therefore, for these
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4 syntheses, another approach was used. To avoid the principal re-designing of flow
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7 system pure THF was added to the third channel and ca ~0.25 M solution of lithiated
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10 pyrazole **11x** in THF formed in the batch variant. For **11c** ~0.25 M solution of **11x** was
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13 collected into the reactor containing 2-fold excess of dry ice. After the reaction completion
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16 at room temperature and evaporation of the excess of CO₂ the desired acid **11c** was
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19 isolated in 78% yield. For the efficient synthesis of lithium pyrazolylsulfinate **11e**, the
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22 above-mentioned solution of organolithium **11x** was collected in the batch reactor cooled
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25 to -50 °C. The 5-fold excess of gaseous SO₂ was bubbled through this solution. Then the
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28 reaction mixture was kept at room temperature and the sulfinate **11e** precipitated in 78%
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32 yield. All these processes could be easily scaled up to kilo-scale. Even in the above-
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35 mentioned system the productivity of the processes was 116-152 g/h (Scheme 4, Table
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42 1). Finally, the important building block – corresponding sulfonyl chloride **11f** – was
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45 obtained by batch chlorination of pyrazolylsulfinate **11e** by NCS in DCM at 0 °C in 56%
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48 yield affording more than 30 g of the compound in one synthetic run (Scheme 4).
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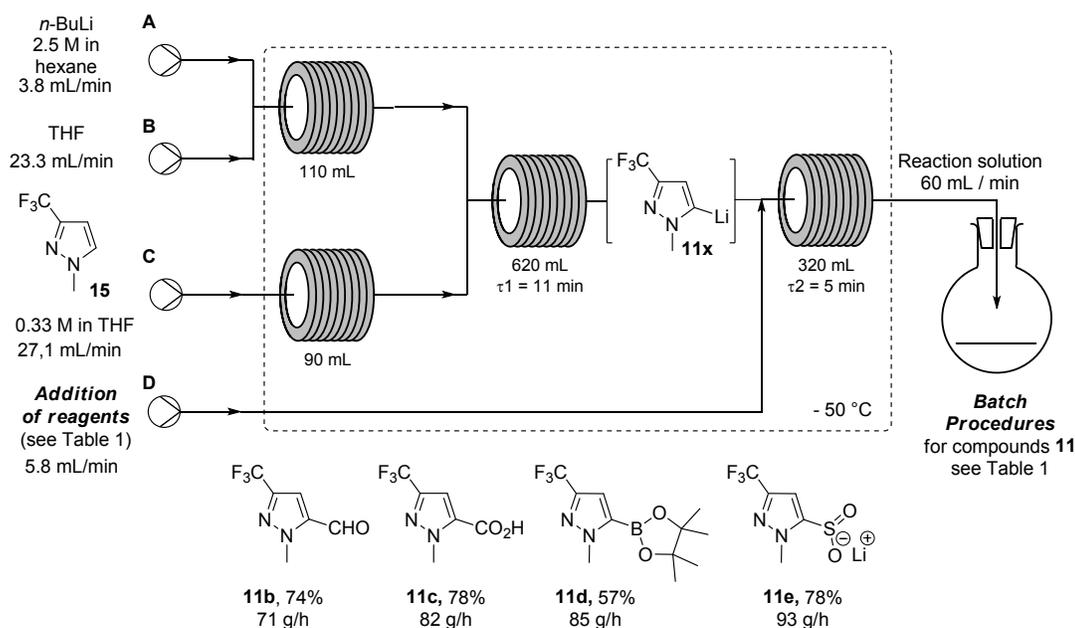
Scheme 4. The synthesis of 5-functionalized 1-methyl-3-(trifluoromethyl)-1*H*-pyrazoles (**3-CF₃-5-FG**) **11** (flow system **A**).

During this part of the project, we met the problem of stable operation of the flow system presented on Scheme 4. Due to the significant misbalance of the flow rates of THF solution of pyrazole **1a** (44 mL/min) and 2.5 M solution of *n*-BuLi (6 mL/min) the system worked stably only for 15-30 min. After this time some problems with temperature control occurred as well as some precipitate formed. Therefore, for a long-time stable operation, we decided to reduce the productivity of the system. In this case, we added 110 mL reactor to the system for the dilution of the 2.5 M solution of *n*-BuLi in hexane by THF at

–50 °C and 90 mL reactor for the pre-cooling of 0.33 M THF solution of pyrazole **1a**. The residence time for the 620 mL and 320 mL reactors was similar to the previous cases.

This system was tested and its behavior was stable during more than 8h operation time.

However, this modification of the system reduced productivity by 38% (Scheme 5).



Scheme 5. Synthesis of the 5-functionalized 1-methyl-3-(trifluoromethyl)-1*H*-pyrazoles

(*3-CF₃-5-FG*) **11** (flow system B).

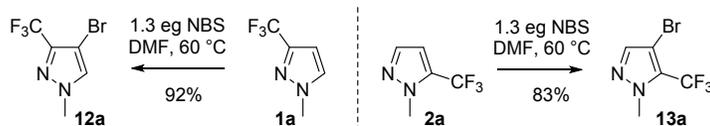
Table 1. Conditions for the flow synthesis of the compounds **11b-e**.

#	Cpd	FG	Additional reagent	Batch procedures	Yield, %	Productivity, g/h (A/B)
1	11b	CHO	2.2 M DMF in THF	1. Saturated NH ₄ Cl 2. Evaporation 3. MTBE-H ₂ O treatment 4 Organic phase evaporation 5. Chromatography SiO ₂ /hexane-MTBE (10:1, R _f = 0.9).	74	116 / 71
2	11c	CO ₂ H	pure THF	1. The reaction solution was collected in a batch with dry ice (~2 eq). 2. The mixture was maintained overnight at rt. 3 After CO ₂ evaporation the residue was treated by DCM-H ₂ O. 4. The water phase was acidified by H ₃ PO ₄ to pH = 2 and the precipitate formed was collected by filtration	78	134 / 82

3	11d	BPin	1.8 M PrOBPin in THF	<p>1. The reaction solution was collected and maintained overnight at rt.</p> <p>2. Evaporation</p> <p>3. MTBE-H₂O treatment</p> <p>4 The organic phase was evaporated</p> <p>5. Chromatography SiO₂/hexane-MTBE (85:15, Rf = 0.85)</p>	57	139 / 85
4	11e	SO ₂ Li	pure THF	<p>1. The reaction solution was collected in a batch cooled to -50 °C.</p> <p>2. The flow of gaseous SO₂ was passed (5-fold excess) through a solution formed.</p> <p>3. The solution was maintained overnight at rt.</p> <p>4. The precipitate formed was collected by filtration and washed by MTBE</p>	78	152 / 93

For the insertion of the functionality into the 4-th position in both regioisomeric trifluoromethylpyrazoles **1a** and **2a** the electrophilic bromination was optimized and scaled up. The bromination of 1.3 M solution of both pyrazoles in DMF by 1.3 eq of NBS at 60 °C during 10h was the optimal condition. Product isolation was provided by vacuum

distillation of the reaction mixture. This developed procedure appears to be more convenient for the scale-up compared to the Schlosser's one, where Br₂/Fe system at 100 °C was utilized.²⁴ When the 200 g of starting pyrazoles **1a** and **2a** were taken the preparative yields of corresponding brominated derivatives **12a** and **13a** were 92% and 83%, respectively (Scheme 6).



Scheme 6. Bromination of trifluoromethylpyrazoles.

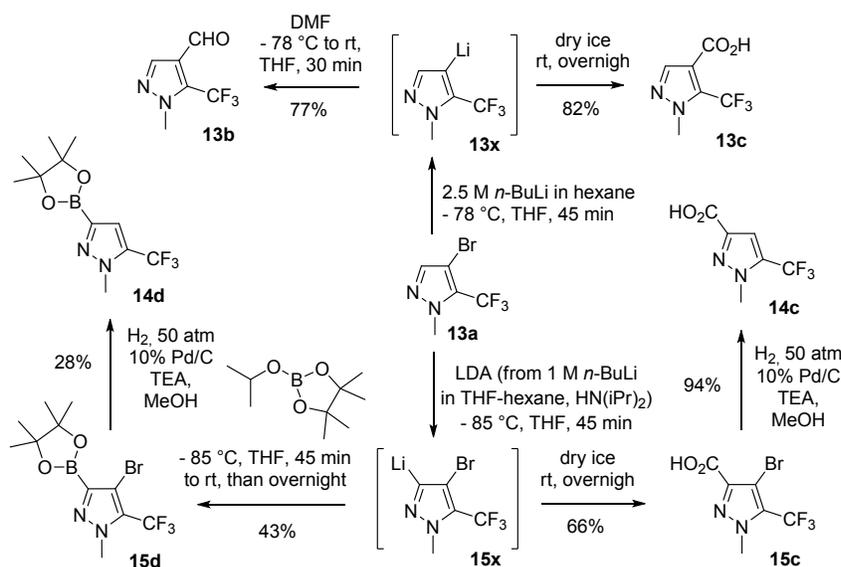
Among two brominated isomers, 4-bromo-5-CF₃ one was chosen for the further Br-Li exchange. In the case of 4-functionalized-3-CF₃ building blocks, the core starting material is the corresponding acid, which is now readily commercially available (according to SciFinder > 10 suppliers propose it in a kilo scale). The route to the acid was based on cyclizations of 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoates with methylhydrazine derivatives and it was developed during *Penthiopyrad* project.³⁰ Previously 4-bromo-1-methyl-5-(trifluoromethyl)pyrazole **13a** was selectively lithiated by *t*-BuLi in Et₂O at -75 °C.²⁴ The lack of such an approach was the use of both *t*-BuLi and Et₂O which was

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3 not a convenient reagent/solvent combination for safe performance, especially in a large
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7 scale. We found that selective Br-Li exchange could be achieved by *n*-BuLi treatment in
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10 THF at -78 °C in a batch reactor. The adaptation of the protocol to the flow reactor failed
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12
13 due to precipitation of the LiBr from the reaction mixture. Generation of the corresponding
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15
16 lithium derivative **13x** was scaled up to 50g of starting bromide **13a** in 2L three-necked
17
18
19 reactor. The subsequent reaction of this organolithium derivative **13x** with DMF or CO₂
20
21
22 afforded the aldehyde **13b** or corresponding acid **13c** in 77% and 82% yields, respectively
23
24
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26
27 (Scheme 7). These examples indicated the perspective of the approach to **5-CF₃-4-FG**
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30 derivatives in scale.
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35 Starting from 4-bromo-1-methyl-5-(trifluoromethyl)pyrazole **13a** we also tested the
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38 multigram scale approach to **5-CF₃-3-FG** derivatives **14** based on DoM lithiation-
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41 functionalization-debromination (see Scheme 2). In seminal Schlosser paper, the DoM
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43
44 lithiation was performed by the reverse addition of the substrate to LDA solution in
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46
47 THF/hexane. We checked if the “normal” addition of LDA solution to the pyrazole **13a**
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49
50 could be performed. It was found, that the reaction proceeded cleanly but at the
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53 temperatures below -85 °C. The process requiring such low temperatures could not be
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3 successfully adapted to flow mode. Using the flow reactor in the conditions typical for
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7 similar purposes (-70 °C to -30 °C, residence time on lithiation step from 5 to 20 min, and
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10 trapping residence from 2 to 10 min) led to the significant formation of the isomeric side
11
12
13 product due to the “halogen dance” reaction.³¹ As in the previous case with Br-Li
14
15
16 exchange, the DoM generation of lithium derivative **15x** was scaled up to 50g of the
17
18 starting bromide **13a** in 2L three-necked reactor but at -85 °C. The trapping of the
19
20 organolithium derivative **15x** by dry ice afforded the corresponding acid **15c** in 66%
21
22 preparative yield. Alternatively, compound **15x** was subjected to the reaction with
23
24 iPrOBPin leading to the corresponding boronic acid pinacolate **15d** formation in 43%
25
26 preparative yield. The structure of the boron derivative was unambiguously determined
27
28 by the single-crystal X-ray diffraction study which proved the absence of the “halogen
29
30 dance” reaction (Scheme 3, Figure 5). For the synthesis of parent *5-CF₃-3-FG* derivatives,
31
32
33 we tested the debromination by catalytic hydrogenation over Pd/C catalyst. In the case of
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35 bromoacid **15c**, the hydrogenation proceeded cleanly at 50 atm in MeOH at the presence
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37 of triethylamine producing the desired product **14c** in 94% preparative yield on 30 g scale.
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60 The similar hydrogenation of brominated boronic acid **15d** was accomplished by

deborylation, but the target pinacolate **14d** could be preparatively isolated in 28% yield on 30 g scale of the starting material (Scheme 7).



Scheme 7. Lithiation of 4-bromo-5- CF_3 -pyrazole.

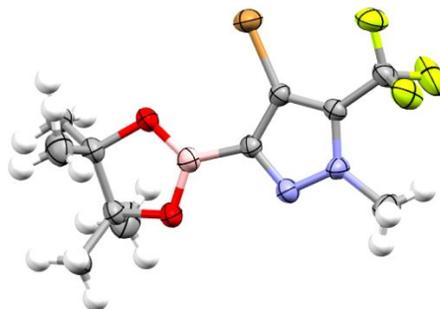
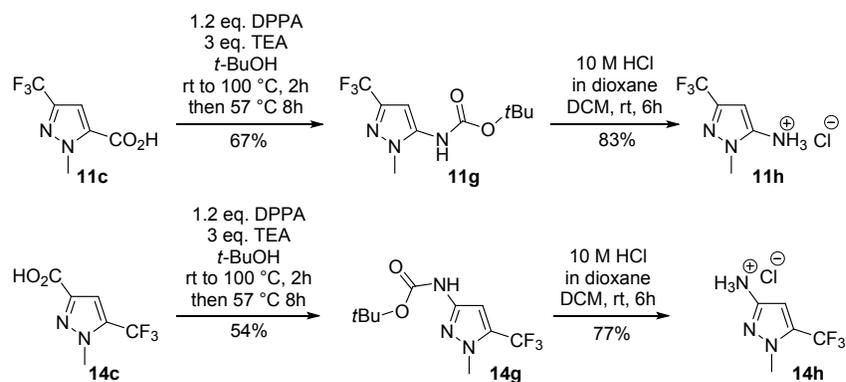


Figure 5. X-ray structure of compound **15d**.³²

In this project, the functional group interconversion was illustrated by Curtius-type rearrangement of two regioisomeric acids **11c** and **14c**. This transformation is important

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3 because the insertion of the amino function *via* lithiated intermediates is problematic due
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7 to the lack of appropriate nitrogen-centered electrophiles. The multigram scale
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10 transformation was performed by DPPA induced Curtius-type rearrangement in *t*-BuOH
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12
13 at the presence of TEA at 100 °C. As a result, the corresponding Boc-protected amines
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17 **11g** and **14g** were formed and isolated in 67% and 54% yield, respectively. The Boc-
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20 deprotection was achieved by treatment in DCM with 10M HCl solution in dioxane. The
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23 final amines **11h** and **14h** were isolated as hydrochlorides in 83% and 77% yields,
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28 respectively (Scheme 8).
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45 **Scheme 8.** Curtius-type rearrangement of pyrazolylcarboxylic acids.
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53 CONCLUSION

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4 In summary, an efficient and practical kilo-scale procedure for 1-methyl-3-
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7 (trifluoromethyl)-1*H*-pyrazole and 1-methyl-5-(trifluoromethyl)-1*H*-pyrazole was
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9
10 developed on the basis of cyclization of 4-ethoxy-1,1,1-trifluoro-3-buten-2-one with
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12
13 methylhydrazine hydrochloride with subsequent regioisomers separation by distillation.
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15
16
17 This protocol opens the door to the active use of these compounds as starting materials
18
19
20 for the design and synthesis of important MedChem and AgroChem relevant building
21
22
23 blocks. For the introduction of the functional group into the 5-th position of 1-methyl-3-
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25
26
27 (trifluoromethyl)-1*H*-pyrazole, the flow lithiation by *n*-BuLi was developed followed with
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30 trapping by the electrophilic reagent. The efficiency of the methodology was proven by
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34 the synthesis of corresponding examples of aldehyde, acid, boron pinacolate and lithium
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36
37 sulfinate in 57-78% yield and productivity 116-152 g/h. The batch mild conditions for the
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39
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41 bromination of both 1-methyl-3-(trifluoromethyl)-1*H*-pyrazole and 1-methyl-5-
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43
44 (trifluoromethyl)-1*H*-pyrazole by NBS were developed and the synthesis was scaled up
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46
47
48 to 200 g in one synthetic run. The Br-Li exchange in 4-bromo-1-methyl-5-
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51 (trifluoromethyl)pyrazole was optimized, and a hazardous combination of *t*-BuLi in Et₂O
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55 was replaced by much more safe *n*-BuLi in THF. Based on the method, the corresponding
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3 aldehyde and acid were synthesized in 50 g scale. Also, in the same scale, the direct
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7 ortho-metalation of the 4-bromo-1-methyl-5-(trifluoromethyl)pyrazole by LDA was
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9
10 developed for the synthesis of the corresponding acid and boron pinacolate. For the
11
12
13 synthesis of "parent" 1-methyl-5-(trifluoromethyl)-1*H*-pyrazoles bearing function in the 3-
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17 rd position, the catalytic hydrogenative debromination of the DoM products was
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20 accomplished. Finally, the handy procedure for the Curtius-type rearrangement leading
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24 to amines was proposed.
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35 EXPERIMENTAL SECTION

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37

38 **General.** The solvents were purified according to the standard procedures. All starting
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41 materials were obtained from Enamine Ltd. Melting points were measured on automated
42
43
44 melting point system. ¹H, ¹³C, and ¹⁹F NMR spectra were recorded on a Bruker 170
45
46
47 Avance 500 spectrometer (at 500 MHz for Protons and 126 MHz for Carbon-13) and
48
49
50 Varian Unity Plus 400 spectrometer (at 400 MHz for protons, 101 MHz for Carbon-13,
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52
53 and 376 MHz for Fluorine-19). Tetramethylsilane (¹H, ¹³C) or C₆F₆ (¹⁹F) were used as
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standards. Elemental analyses were performed at the Laboratory of Organic Analysis, Institute of Organic Chemistry, National Academy of Sciences of Ukraine, their results were found to be in good agreement ($\pm 0.4\%$) with the calculated values. Preparative HPLC analyses were done on an Agilent 1200. Mass spectra were recorded on Agilent 1100 LCMSD SL instrument (chemical ionization (APCI)). CCDC-2011680 (**15d**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

The synthesis and separation of 1-methyl-3-(trifluoromethyl)-1H-pyrazole (1a) and 1-methyl-5-(trifluoromethyl)-1H-pyrazole (2a).

The solution of 4-ethoxy-1,1,1-trifluorobut-3-en-2-one (5.30 kg, 31.5 mol) in methanol (10 L) was loaded into 30 L reactor and brought to a boiling. To this refluxed solution the solution of $\text{NH}_2\text{NH}_2\cdot\text{HCl}$ (2.860 kg, 41.7 mol) in water (7.5 L) was added during 1.5 h. When the addition finished, the reaction mixture was refluxed for additional 1h. Then it was cooled to rt, transferred to an extractor, and 20L of water was added with stirring. The mixture obtained was stirred for 10 min and left to stand overnight for the phases

1
2
3 separation. The organic phase was separated and dried over Na₂SO₄ overnight (100 g of
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7 sulfate for 1 kg of the desired product). This crude mixture (consisting of 3-CF₃ and 5-CF₃
8
9
10 isomers in 0.7:1 ratio) was transferred into the 5L round bottom distillation apparatus with
11
12
13
14 25 cm fractioning column, and fractioned at atmospheric pressure. Three fractions were
15
16
17 collected: 55-75 °C, ca 200g (methanol, ethanol and small amount of 5-CF₃ isomer); 75-
18
19
20 125 °C, 2.4 kg (5-CF₃ and 3-CF₃ isomers in 1:0.2 ratio); 125-155 °C, ca 300 g (3-CF₃ and
21
22
23
24 5-CF₃ isomers in 1:1 ratio). The residue after such distillation contained only raw 3-CF₃
25
26
27
28 isomer. This residue was distilled using the vacuum pump (Ilmvac Gardner Denver MPC
29
30
31 301 Zp, 230V 50/60Hz with the pressure down to 8 mbar) at 32-55 °C. The collector was
32
33
34 cooled by the ice-ethanol mixture. The collected raw 3-CF₃ isomer was dried over P₂O₅
35
36
37
38 (20 g of oxide per 1 kg of the desired product) and re-distilled using the same vacuum
39
40
41
42 pump at 42-43 °C affording pure compound **1a** as a colorless liquid (1.5 kg, 31.7%). The
43
44
45 second fraction after the first distillation bearing the mixture of 3-CF₃ and 5-CF₃ isomers
46
47
48
49 in 0.2:1 ratio was transferred into the 4L round bottom distillation apparatus with 25 cm
50
51
52 fractioning column. Then it was distilled at atmospheric pressure keeping the bath
53
54
55
56 temperature 135 °C. The collected fraction (2.0 kg) at 95-102 °C contained the raw 5-CF₃
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60

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3 isomer and the residue (~150g) was the crude mixture of 3-CF₃ and 5-CF₃ isomers in 1:1
4
5
6
7 ratio. The collected raw 3-CF₃ isomer was dried over P₂O₅ (20 g of oxide per 1 kg of the
8
9
10 desired product) and distilled using the vacuum pump cited above at 34-35 °C. The
11
12
13
14 obtained distillate was cooled by the ice-ethanol mixture affording pure compound **2a** as
15
16
17 a colorless liquid (1.8 kg, 38.1%)
18
19
20

21 **1-methyl-3-(trifluoromethyl)-1H-pyrazole (1a)**: colorless liquid. ¹H NMR (400 MHz,
22
23 Chloroform-*d*) δ 7.37 (s, 1H), 6.48 (d, *J* = 2.3 Hz, 1H), 3.93 (s, 3H). ¹³C NMR (126 MHz,
24
25 Chloroform-*d*) δ 142.4 (q, *J* = 38.0 Hz), 131.3, 121.3 (q, *J* = 267.9, 267.5 Hz), 104.5, 39.4.
26
27
28 ¹⁹F NMR (376 MHz, Chloroform-*d*) δ -62.4. EIMS, 70eV, *m/z* (rel. int.): 151 [M+H]⁺ (6);
29
30
31
32 150 [M]⁺ (100); 149 (43); 131 (35); 129 (12); 81 (11); 69 (19); 54 (17); 52 (12); 42 (17).
33
34
35
36
37
38 Anal. calcd. for C₅H₅F₃N₂: C, 40.01; H, 3.36; N, 18.66. Found: C, 39.63; H, 3.56; N, 18.56.
39
40
41

42 **1-methyl-5-(trifluoromethyl)-1H-pyrazole (2a)**: colorless liquid. ¹H NMR (400 MHz,
43
44 DMSO-*d*₆) δ 7.61 (s, 1H), 6.86 (s, 1H), 3.96 (s, 3H). ¹³C NMR (126 MHz, DMSO-*d*₆) δ
45
46
47 138.7, 130.8 (q, *J* = 38.6 Hz), 120.6 (q, *J* = 268.2 Hz), 108.4 (q, *J* = 2.4 Hz), 38.3. ¹⁹F
48
49
50
51
52 NMR (376 MHz, DMSO-*d*₆) δ -59.5. EIMS, 70eV, *m/z* (rel. int.): 151 [M+H]⁺ (7); 150 [M]⁺
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3
4 (100); 149 (41); 131 (34); 129 (12); 69 (12); 54 (12); 42 (12). Anal. calcd. for C₅H₅F₃N₂:
5
6
7 C, 40.01; H, 3.36; N, 18.66. Found: C, 39.88; H, 3.09; N, 19.03.
8
9

10 *Flow Chemistry Process for 1-methyl-3-(trifluoromethyl)-1H-pyrazole 1a lithiation.*

11
12
13
14 Four pumps (Masterflex L/S peristaltic pumps with pump heads for PTFE tubing) were
15
16
17 used to pump the solutions of the three reagents (see Scheme 5). The feedstock **A** was
18
19
20 commercially available 2.5 M n-BuLi in hexane used directly from the supplied bottle and
21
22
23 pumped at 3.8 mL/min. The feedstock **B** was THF (pumped at 23.3 mL/min to dilute
24
25
26 feedstock **A** inflow). The feedstock **C** consisted of 1-methyl-5-(trifluoromethyl)-1H-
27
28
29 pyrazole **1a** dissolved in anhydrous THF as a 0.33 M solution; it was pumped at 21.7
30
31
32 mL/min. The feedstock **D** contained different reagents (see Table 1) and pumped at 5.8
33
34
35 mL/min. All feedstocks were maintained under an atmosphere of argon. The reactors
36
37
38 were fabricated from Altafluor 400 (PFA) tubing with an ID of 3/16 in a length of 34.6 m
39
40
41 for the lithiation stage or the length of 17.3 m for the second stage. The residence time
42
43
44 for the lithiation step was set to 12 min and the second step residence time was 5 min.
45
46
47
48 Swagelok SS-400-3-4-TTF tees and Koflo1/4-40-3-12-2 static mixers (total internal
49
50
51 volume 20 ml) were used. The pre-cooling loops (L = 5.2 m, ID = 3/16 in) and reactors for
52
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2
3 both the lithiation and electrophilic reaction steps were submerged into a cooling bath set
4
5
6
7 at -50 °C before initiating the three pumps. The temperature in the plug flow reactors was
8
9
10 monitored and maintained at approximately -50 °C. After a steady flow was attained the
11
12
13 product stream was collected and treated as indicated below.
14
15

16
17 *1-Methyl-3-(trifluoromethyl)-1H-pyrazole-5-carbaldehyde (11b).*
18
19

20
21 The feedstock **D** was 2.2 M DMF in THF. The collected product stream from the FC
22
23
24 (after 4 h of system operation) process was quenched with saturated aq. NH₄Cl (600 mL).
25
26

27
28 The solvent was evaporated in vacuo using a rotary evaporator. The residue was mixed
29
30
31 with MTBE-water (3:1, 1.6 L) and extracted with MTBE (2x250mL). The organic phase
32
33
34 was separated and washed with brine (5x300 mL) and dried over Na₂SO₄ (220 g). The
35
36
37 solvents were evaporated and the residue was dissolved in n-hexane (300 mL) and
38
39
40 passed through SiO₂ using 4L Schott filter funnel (L = 0.30 m, ID = 0.15 m) loaded with
41
42
43 SiO₂ (1.7 kg) and n-hexane-MTBE, 10:1 as eluent (20 L) affording compound **11b** (R_f (n-
44
45
46 hexane-MTBE, 10:1) = 0.9) as pale yellow liquid that crystallized over time (220 g, 74%).
47
48
49
50

51
52 Yellow crystalline powder. M.p. = 26-27 °C. ¹H NMR (400 MHz, Chloroform-*d*) δ 9.89
53
54
55 (s, 1H), 7.15 (s, 1H), 4.24 (s, 3H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 179.2, 141.7 (q,
56
57
58
59
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3
4 $J = 39.3$ Hz), 139.8, 120.5 (q, $J = 268.6$ Hz), 112.4 (q, $J = 2.3$ Hz), 40.19. ^{19}F NMR (376
5
6
7 MHz, Chloroform- d) δ -62.8. EIMS, 70eV, m/z (rel. int.): 179 $[\text{M}]^+$ (7); 178 $[\text{M}]^+$ (100); 177
8
9
10 (59); 159 (25); 149 (15); 81 (17); 80 (10); 69 (10); 52 (10). Anal. calcd. for $\text{C}_6\text{H}_5\text{F}_3\text{N}_2\text{O}$: C,
11
12
13 40.46; H, 2.83; N, 15.73. Found: C, 40.65; H, 2.99; N, 15.80.

14
15
16
17 *1-Methyl-3-(trifluoromethyl)-1H-pyrazole-5-carboxylic acid (11c).*
18
19

20
21 The feedstock **D** was pure THF. The product stream from the FC (after 4 h of system
22
23 operation) process was collected into a batch reactor loaded with dry ice (1.5 kg) before
24
25 initiating the three pumps. Then the reaction mixture obtained was maintained with stirring
26
27 at rt 10h. The solvent was evaporated in vacuo using a rotary evaporator. The residue
28
29 was mixed with DCM-water (1:4, 2 L) and extracted with DCM (2x350 mL). The water
30
31 phase was separated and acidified by 85% aq. H_3PO_4 to pH = 2. The precipitate formed
32
33 was collected by filtration and dried on air during 48 h affording the acid **11c** (HPLC purity
34
35 96.5%, 252 g, 78%).
36
37
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49 Yellow crystalline powder. M.p. = 132 °C. ^1H NMR (400 MHz, Chloroform- d) δ 11.58
50
51 (br, 1H), 7.25 (s, 1H), 4.29 (s, 3H). ^{13}C NMR (126 MHz, Chloroform- d) δ 163.5, 141.2 (q,
52
53
54
55 $J = 39.4$ Hz), 132.9, 120.5 (q, $J = 268.8$ Hz), 111.1 (q, $J = 2.3$ Hz), 40.6. ^{19}F NMR (376
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4 MHz, Chloroform-*d*) δ -62.9. LCMS, negative mode, *m/z*: 193 [M-H]⁻. Anal. calcd. for

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6
7 C₆H₅F₃N₂O₂: C, 37.13; H, 2.60; N, 14.43. Found: C, 37.08; H, 2.25; N, 14.53.

8
9
10
11 *1-Methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)-1H-*
12
13
14 *pyrazole (11d).*

15
16
17 The feedstock **D** was 1.8 M iPrOBPin in THF. The collected product stream from the
18
19
20
21 FC (after 4h of system operation) process was maintained with stirring at rt 10h and then
22
23
24 quenched with saturated NH₄Cl (600 mL). The solvent was evaporated in vacuo using a
25
26
27 rotary evaporator. The residue was mixed with MTBE-water (3:1, 1.6 L) and extracted
28
29
30
31 with MTBE (2x250 mL). The organic phase was separated and washed with saturated aq
32
33
34 NaHCO₃ (1x500 mL) and dried over Na₂SO₄ (220 g). Solvents was evaporated and the
35
36
37
38 residue was dissolved in n-hexane (300 mL) and passed through SiO₂ using 4L Schott
39
40
41 filter funnel (L = 0.30 m, ID = 0.15 m) loaded with SiO₂ (1.7 kg) and n-hexane-MTBE,
42
43
44
45 85:15 as eluent (15 L) affording compound **11d** with R_f = 0.85 as pale-yellow crystals
46
47
48
49 (263 g, 57%).

50
51
52 Yellow crystalline powder. M.p. = 64-68 °C. ¹H NMR (400 MHz, Chloroform-*d*) δ 6.96
53
54
55
56 (s, 1H), 4.13 (s, 3H), 1.36 (s, 12H). ¹³C NMR (151 MHz, Chloroform-*d*) δ 141.6 (q, *J* =
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58
59
60

1
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3 38.0 Hz), 135.6, 121.4 (q, $J = 268.2$ Hz), 114.1 (q, $J = 2.2$ Hz), 84.7, 40.0, 24.7. ^{19}F NMR
4
5
6
7 (376 MHz, Chloroform- d) δ -62.2. EIMS, 70eV, m/z (rel. int.): 277 $[\text{M}+\text{H}]^+$ (7); 276 $[\text{M}]^+$
8
9
10 (58); 275 (16); 262 (11); 261 (100); 260 (26); 257 (21); 233 (11); 219 (24); 191 (12); 190
11
12
13 (72); 177 (47); 176 (18); 165 (20); 157 (15); 85 (13); 59 (27); 58 (25); 57 (18); 43 (43); 42
14
15
16
17 (30); 41 (31); 39 (12). Anal. calcd. for $\text{C}_{11}\text{H}_{16}\text{BF}_3\text{N}_2\text{O}_2$: C, 47.86; H, 5.84; N, 10.15. Found:
18
19
20
21 C, 47.99; H, 6.21; N, 9.96.
22
23

24 *Lithium 1-methyl-3-(trifluoromethyl)-1H-pyrazole-5-sulfinate (11e).*
25
26
27

28 Feedstock **D** was pure THF. The product stream from the FC (after 4 h of system
29
30
31 operation) process was collected in batch reactor cooled to -50 °C. The stream of gaseous
32
33
34 SO_2 (5-fold excess, 267 g, 4.16 mol) was bubbled through this mixture from the damper
35
36
37 camera. The reaction mixture was allowed to warm to rt and was maintained with stirring
38
39
40
41
42 10h. The precipitate formed was collected by filtration, washed with MTBE (3x200 mL)
43
44
45 and dried in vacuo (1 mmHg, rt) affording sulfinate **11e** (HPLC purity 95.2%, 143 g, 78%).
46
47
48

49 White powder. M.p. = 267-274 °C. ^1H NMR (400 MHz, DMSO- d_6) δ 6.45 (s, 1H), 3.96
50
51
52 (s, 3H). ^{13}C NMR (126 MHz, DMSO- d_6) δ 160.2, 138.3 (q, $J = 36.8$ Hz), 122.3 (q, $J =$
53
54
55 268.1 Hz), 101.7 (q, $J = 2.3$ Hz), 38.0. ^{19}F NMR (376 MHz, DMSO- d_6) δ -60.5. LCMS,
56
57
58
59
60

1
2
3
4 negative mode, m/z: 213 [M-Li]⁻. Anal. calcd. for C₅H₄F₃LiN₂O₂S: C, 27.29; H, 1.83; N,
5
6
7 12.73; S, 14.57. Found: C, 27.24; H, 1.56; N, 12.44; S, 14.35.
8
9

10
11 *1-Methyl-3-(trifluoromethyl)-1H-pyrazole-5-sulfonyl chloride (11f)*
12

13
14 Sulfinic acid **11e** (50g, 0.23 mol) was suspended in dry DCM (1 L). NCS (33.4 g, 0.25 mol)
15
16
17 was added to the stirred suspension by portions for 20 min at 0 °C. The reaction mixture
18
19
20 was stirred at rt 6h and then washed with water (3x250 mL) and saturated NaHCO₃
21
22
23 (3x350 mL) and dried over Na₂SO₄ (100 g). The solvent was evaporated and the residue
24
25
26 was subjected to flash column chromatography over SiO₂ using *n*-hexane-MTBE 85:15
27
28
29 affording compound **11f** with R_f = 0.8 as a colorless liquid (31.7 g, 56%).
30
31
32

33
34
35 Colorless liquid. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.27 (s, 1H), 4.30 (s, 3H). ¹³C NMR
36
37
38 (126 MHz, Chloroform-*d*) δ 142.5, 141.2 (q, *J* = 40.4 Hz), 119.8 (q, *J* = 269.6 Hz), 110.2
39
40
41 (q, *J* = 2.2 Hz), 39.9. ¹⁹F NMR (376 MHz, Chloroform-*d*) δ -63.0. LCMS, negative mode,
42
43
44 m/z: 229 [M-H₂O-H]⁻. Anal. calcd. for C₅H₄ClF₃N₂O₂S: C, 24.16; H, 1.62; N, 11.27; S,
45
46
47 12.90; Cl, 14.26. Found: C, 23.84; H, 1.71; N, 10.89; S, 13.12; Cl, 14.23.
48
49
50

51
52 *General protocol for the bromination of 1-methyl-3-(trifluoromethyl)-1H-pyrazole (1a)*
53
54
55
56 *and 1-methyl-5-(trifluoromethyl)-1H-pyrazole (2a)*
57
58
59
60

1
2
3 The corresponding pyrazole (200.0 g, 1.33 mol) was mixed with DMF (1 L) in 4L round
4
5
6
7 bottom reactor. Then NBS (296.5g, 1.66 mol) was added to the mixture. The mixture was
8
9
10 heated to 60 °C and stirred 10h. Then the mixture was cooled to rt and water was added
11
12
13 (3 L). The solution formed was extracted with MTBE (3x0.7 L). The organic phase was
14
15
16
17 separated, washed with brine (5x0.5 L) and saturated aqueous Na₂SO₃ (2x250 mL). The
18
19
20 solvents were evaporated in vacuo and the residue was distilled using oil pump (2 mmHg)
21
22
23
24 affording desired compounds as colorless liquids.
25
26
27

28 *4-Bromo-1-methyl-3-(trifluoromethyl)-1H-pyrazole (12a)*.

29
30
31 Yield = 92% (281.0 g). White crystalline powder. ¹H NMR (400 MHz, Chloroform-*d*) δ
32
33
34 7.47 (s, 1H), 3.95 (s, 3H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 140.2 (q, *J* = 37.5 Hz),
35
36
37
38 132.7, 120.6 (q, *J* = 269.4 Hz), 91.5, 40.0. ¹⁹F NMR (376 MHz, Chloroform-*d*) δ -62.5.
39
40
41
42 EIMS, 70eV, *m/z* (rel. int.): 230 [M+H]⁺ (97); 229 [M]⁺ (20); 228 (100); 227 (15); 211 (15);
43
44
45 209 (20); 69 (16); 42 (26). Anal. calcd. for C₅H₄BrF₃N₂: C, 26.22; H, 1.76; N, 12.23; Br,
46
47
48 34.89. Found: C, 26.59; H, 1.63; N, 11.95; Br, 34.86.
49
50
51

52 *4-Bromo-1-methyl-5-(trifluoromethyl)-1H-pyrazole (13a)*.

1
2
3 Yield = 83% (253.0 g). Colorless liquid. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.48 (s,
4
5
6
7 1H), 4.02 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 140.2, 129.3 (q, J = 38.4 Hz),
8
9
10 119.8 (q, J = 270.1 Hz), 95.3, 39.7. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -59.1. EIMS,
11
12
13 70eV, m/z (rel. int.): 230 $[\text{M}+\text{H}]^+$ (97); 229 $[\text{M}]^+$ (33); 228 (100); 209 (11); 80 (12); 69 (22);
14
15
16
17 43 (11). Anal. calcd. for $\text{C}_5\text{H}_4\text{BrF}_3\text{N}_2$: C, 26.22; H, 1.76; N, 12.23; Br, 34.89. Found: C,
18
19
20 26.34; H, 1.79; N, 12.38; Br, 34.70.
21
22
23

24 *1-Methyl-5-(trifluoromethyl)-1H-pyrazole-4-carbaldehyde (13b)*
25
26
27

28 The 2L three-necked reactor was loaded with the solution of 4-bromo-1-methyl-3-
29
30 (trifluoromethyl)-1H-pyrazole **13a** (50 g, 0.22 mol) in THF (500 mL) and 2.5 M n-BuLi in
31
32 hexane (92 mL, 0.23 mol) was added dropwise at -78 °C. The reaction mixture was
33
34
35 maintained at -78 °C during 45 min and the solution of DMF (23 mL, 0.3 mol) in THF (100
36
37
38 mL) was added dropwise at the same temperature. The mixture was maintained for 30
39
40
41 min and quenched with saturated NH_4Cl (300 mL). The solvent was evaporated in vacuo
42
43
44 using a rotary evaporator. The residue was mixed with MTBE-water (4:1, 1.25 L) and
45
46
47 extracted with MTBE (2x200 mL). The organic phase was separated and washed with
48
49
50 brine (5x300 mL) and dried over Na_2SO_4 (180 g). The solvents were evaporated and the
51
52
53
54
55
56
57
58
59
60

1
2
3 residue was subjected to flash column chromatography over SiO₂ using n-hexane-MTBE
4
5
6
7 10:1 affording compound **13b** with R_f = 0.85 as white crystals (29.9 g, 74%).
8
9

10 White crystals. M.p. = 59 °C. ¹H NMR (400 MHz, Chloroform-*d*) δ 10.03 (s, 1H), 8.00
11
12 (s, 1H), 4.07 (s, 3H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 183.00 (q, *J* = 3.2 Hz), 139.3,
13
14 133.0 (q, *J* = 40.4, 40.0 Hz), 123.5, 119.8 (q, *J* = 270.7 Hz), 39.0 (d, *J* = 2.6 Hz). ¹⁹F NMR
15
16 (376 MHz, Chloroform-*d*) δ -58.3. EIMS, 70eV, *m/z* (rel. int.): 178 [M]⁺ (50); 177 (100).
17
18
19
20
21
22
23
24 Anal. calcd. for C₆H₅F₃N₂O: C, 40.46; H, 2.83; N, 15.73. Found: C, 40.45; H, 3.09; N,
25
26
27 15.33.
28
29
30

31 *1-Methyl-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (13c)*.
32
33

34
35 The 2L three-necked reactor was loaded by solution of 4-bromo-1-methyl-3-
36
37 (trifluoromethyl)-1*H*-pyrazole **13a** (50 g, 0.22 mol) in THF (500 mL) and 2.5 M n-BuLi in
38
39 hexane (92 mL, 0.23 mol) was added dropwise at -78 °C. The reaction mixture was
40
41
42 maintained at -78 °C for 45 min and then was poured on dry ice (96 g, 2.18 mol). Then
43
44
45 the reaction mixture obtained was maintained for 10h with stirring at rt. The solvent was
46
47
48
49 evaporated in vacuo using a rotary evaporator. The residue was mixed with DCM-water
50
51
52 (1:4, 1.25 L) and extracted with DCM (2x250 mL). The water phase was separated and
53
54
55
56
57
58
59
60

1
2
3 acidified by 85% aq. H₃PO₄ to pH = 2. The precipitate formed was collected by filtration
4
5
6
7 and dried on air during 48h affording acid **13c** (HPLC purity 97.3%, 34.7g, 82%).
8
9

10 Yellow powder. M.p. = 120 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.08 (s, 1H), 7.96 (s,
11
12 1H), 4.05 (s, 3H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 162.2, 141.5, 131.0 (q, *J* = 39.7 Hz),
13
14 120.0 (q, *J* = 270.4 Hz), 116.8, 40.8. ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -56.5. LCMS,
15
16
17 positive mode, *m/z*: 195 [M+H]⁺. Anal. calcd. for C₆H₅F₃N₂O₂: C, 37.13; H, 2.60; N, 14.43.
18
19
20
21 Found: C, 36.78; H, 2.80; N, 14.21.
22
23
24
25
26
27

28 *4-Bromo-1-methyl-5-(trifluoromethyl)-1H-pyrazole-3-carboxylic acid (15c).*
29
30

31 The 2L three-necked reactor was loaded with the solution of 4-bromo-1-methyl-3-
32
33 (trifluoromethyl)-1*H*-pyrazole **13a** (50 g, 0.22 mol) in THF (500 mL) and the solution of
34
35 LDA (previously prepared from 2.5M n-BuLi in hexane (92 mL, 0.23 mol) and *i*-Pr₂NH
36
37 (24.3 g, 0.24 mol) in THF (200 mL)) was added dropwise at -85 °C. The reaction mixture
38
39
40
41
42 was maintained at -85 °C for 45 min and then was poured on dry ice (96 g, 2.18mol).
43
44
45
46
47
48
49 Then the reaction mixture obtained was maintained for 10h with stirring at rt. The solvent
50
51
52 was evaporated in vacuo using a rotary evaporator. The residue was mixed with DCM-
53
54
55
56 water (1:3, 12 L) and extracted with DCM (2x250mL). The water phase was separated
57
58
59
60

1
2
3 and acidified by 85% aq. H₃PO₄ to pH = 2. The precipitate formed was collected by
4
5
6 filtration and dried on air during 48h affording acid **15c** (HPLC purity 97.5 %, 39.6 g, 66%).
7
8

9
10 Yellow powder. M.p. = 144 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.44 (s, 1H), 4.07 (s,
11
12 3H). ¹³C NMR (126 MHz, DMSO-*d*₆) δ 161.5, 140.9, 130.7 (q, *J* = 37.4 Hz), 119.7 (q, *J* =
13
14 270.6 Hz), 97.8 (q, *J* = 2.2 Hz), 41.4 (q, *J* = 2.7 Hz). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -
15
16
17 58.2. LCMS, negative mode, m/z: 271 [M-2H]⁻. Anal. calcd. for C₆H₄BrF₃N₂O₂: C, 26.40;
18
19
20
21 H, 1.48; N, 10.26; Br, 29.27. Found: C, 26.41; H, 1.79; N, 9.94; Br, 29.31.
22
23
24
25
26

27
28 *4-Bromo-1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)-*
29
30
31 *1H-pyrazole (15d).*
32
33

34
35 The 2L three-necked reactor was loaded with the solution of 4-bromo-1-methyl-3-
36
37 (trifluoromethyl)-1*H*-pyrazole **13a** (50 g, 0.22 mol) in THF (500 mL) and the solution of
38
39 LDA (previously prepared from 2.5M n-BuLi in hexane (92 mL, 0.23 mol) and i-Pr₂NH
40
41 (24.3 g, 0.24 mol) in THF (200 mL)) was added dropwise at -85 °C. The reaction mixture
42
43
44
45
46
47
48 was maintained at -85 °C for 45 min and then the *t*PrOBPin was added dropwise at the
49
50
51
52
53
54
55
56
57
58
59
60 quenched with saturated NH₄Cl (250 mL). The solvent was evaporated in vacuo using a

1
2
3 rotary evaporator. The residue was mixed with MTBE-water (4:1, 1.25L) and extracted
4
5
6
7 with MTBE (2x250 mL). The organic phase was separated and washed with saturated aq
8
9
10 NaHCO₃ (2x400mL) and dried over Na₂SO₄ (180 g). The solvents were evaporated and
11
12
13 the residue was subjected to column chromatography over SiO₂ using n-hexane-MTBE
14
15
16
17 85:15 affording compound **15d** with R_f = 0.85 as white crystals (33.2 g, 43%).
18
19
20

21 White crystalline powder. M.p. = 105 °C. ¹H NMR (400 MHz, Chloroform-*d*) δ 4.08 (t, *J*
22
23 = 1.5 Hz, 3H), 1.38 (s, 12H). ¹³C NMR (151 MHz, Chloroform-*d*) δ 143.2, 130.0 (q, *J* =
24
25 37.8 Hz), 119.9 (q, *J* = 270.3 Hz), 103.1, 84.5, 40.0 (q, *J* = 2.4 Hz), 24.8. ¹⁹F NMR (376
26
27 MHz, Chloroform-*d*) δ -58.9. EIMS, 70eV, m/z (rel. int.): 357 (9); 355 [M]⁺ (96); 354 (73);
28
29 353 (88); 352 (91); 352 (19); 342 (10); 340 (94); 339 (100); 337 (20); 335 (20); 323 (45);
30
31 321 (43); 320 (12); 313 (62); 311 (64); 310 (16); 299 (14); 297 (17); 275 (48); 274 (14);
32
33 273 (11); 270 (15); 267 (15); 257 (78); 256 (49); 255 (90); 253 (46); 252 (12); 237 (10);
34
35 235 (12); 233 (48); 232 (14); 219 (10); 177 (13); 110 (24); 85 (62); 82 (54); 69 (21); 67
36
37 (39); 59 (31); 58 (15); 57 (25); 55 (13); 43 (73); 41 (66); 39 (25). Anal. calcd. for
38
39 C₁₁H₁₅BBrF₃N₂O₂: C, 37.22; H, 4.26; N, 7.89; Br, 22.51. Found: C, 37.06; H, 4.38; N,
40
41 8.07; Br, 22.90.
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3
4 *1-Methyl-5-(trifluoromethyl)-1H-pyrazole-3-carboxylic acid (14c).*
5
6

7 The 3L autoclave equipped with mechanical stirring was loaded with the solution of
8
9
10 bromo derivative **15c** (27.2 g, 0.1 mol) in MeOH (600 mL). TEA (28 mL, 0.2 mol) and 10%
11
12
13 Pd/C (5.3 g, 5 mmol) was added to the mixture formed. The mixture was treated at 50
14
15
16 atm of hydrogen pressure at 20 °C during 24h. The precipitate formed was filtered off.
17
18
19
20
21 The solvent was evaporated in vacuo. The residue was mixed with DCM-water (3:1, 800
22
23
24 mL) and acidified with 2M aq. HCl to pH = 2. The solution was extracted with DCM (2x150
25
26
27 mL). The organic phase was separated, dried over Na₂SO₄ (100 g) and the solvent was
28
29
30
31 evaporated in vacuo affording acid **14c** (HPLC purity 98.1%, 18.2 g, 94%).
32
33

34
35 Yellow powder. M.p. = 125 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.18 (s, 1H), 7.27 (s,
36
37 1H), 4.03 (s, 3H). ¹³C NMR (126 MHz, DMSO-*d*₆) δ 162.3, 143.2, 132.3 (q, *J* = 39.4 Hz),
38
39 119.8 (q, *J* = 269.0 Hz), 110.7 (q, *J* = 2.5 Hz), 39.3 (q, *J* = 1.8 Hz). ¹⁹F NMR (376 MHz,
40
41 DMSO-*d*₆) δ -59.9. LCMS, negative mode, *m/z*: 193 [M-H]⁻. Anal. calcd. for C₆H₅F₃N₂O₂:
42
43
44
45
46
47
48
49 C, 37.13; H, 2.6; N, 14.43. Found: C, 37.18; H, 2.25; N, 14.22.
50
51

52 *1-Methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)-1H-*
53
54
55
56 *pyrazole (14d).*
57
58
59
60

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2
3
4 The 3L autoclave equipped with mechanical stirring was loaded with the solution of
5
6
7 bromo derivative **14d** (35.5 g, 0.1 mol) in MeOH (600 mL). TEA (28 mL, 0.2 mol) and 10%
8
9
10 Pd/C (5.3 g, 5 mmol) was added to the mixture formed. The mixture was treated at 50
11
12
13 atm of hydrogen pressure at 20°C during 4h. The precipitate formed was filtered off. The
14
15
16 solvents were evaporated in vacuo and the residue was mixed with DCM (400mL) and
17
18
19 10% aq citric acid (200 mL). The organic phase was separated and dried over Na₂SO₄
20
21
22 (120 g). The solvents were evaporated and the residue was subjected to column
23
24
25 chromatography over SiO₂ using n-hexane-MTBE 4:1 affording compound **14d** with R_f =
26
27
28 0.8 as a pale-yellow liquid that crystallized over time (7.7 g, 28%).
29
30
31
32
33

34
35 Yellow crystals. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.71 (s, 1H), 4.02 (s, 3H), 1.32 (s,
36
37
38 12H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 144.9, 135.7 (q, *J* = 39.6 Hz), 120.4 (q, *J* =
39
40
41 270.1 Hz), 100.7, 83.8, 38.5 (q, *J* = 2.7 Hz), 24.7. ¹⁹F NMR (376 MHz, Chloroform-*d*) δ -
42
43
44 58.6. LCMS, positive mode, *m/z*: 277 [M+H]⁺. Anal. calcd. for C₁₁H₁₆BF₃N₂O₂: C, 47.86;
45
46
47 H, 5.84; N, 10.15. Found: C, 48.00; H, 5.74; N, 9.86.
48
49
50

51
52 *General protocol for the Curtius-type rearrangement of pyrazolylcarbonic acids.*
53
54
55
56
57
58
59
60

1
2
3 **Step 1.** The corresponding acid **11c** or **14c** (19.4 g, 0.1 mol) was dissolved in *t*-BuOH
4 (200 mL) in the 1L round bottom reactor and TEA (41.8 mL, 0.3 mol) was added. DPPA
5
6 (26 mL, 0.12 mol) was dropwise slowly added to the stirred mixture. The reaction mixture
7
8 was very slowly heated to 100 °C (during 2-3 h) on an oil bath to observe the gas
9
10 evolution. **CAUTION!** Take care of the intensity of gas evolution. It should be stable and
11
12 not very intense. When the temperature reached 100 °C, the reaction mixture was
13
14 maintained at for 1 additional hour. Then the mixture was cooled to room temperature
15
16 and the solvent was evaporated in vacuo. The residue was mixed with MTBE – 30% aq
17
18 K₂CO₃ (1:2; 1.2 L) and the precipitate formed was filtered off. This manipulation was
19
20 repeated 3 times. Then the combined water phase was separated and extracted with
21
22 MTBE (3x200 mL). The organic phase was separated and washed with water (3x250 mL)
23
24 and dried over Na₂SO₄ (120 g). The solvent was evaporated and the residue was
25
26 subjected to column chromatography over SiO₂ using MTBE as eluent affording the
27
28 desired compounds **11g** and **14g**. The obtained compounds can be used in the next step
29
30 without additional purification.
31
32
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54
55
56 *Tert-butyl (1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)carbamate (11g).*
57
58
59
60

1
2
3 White powder. Yield = 67% (18.3 g). $R_f = 0.95$ (MTBE). ^1H NMR (400 MHz, Chloroform-
4 d) δ 6.70 (br, 1H), 6.39 (s, 1H), 3.75 (s, 3H), 1.48 (s, 9H). ^{13}C NMR (151 MHz, Chloroform-
5 d) δ 152.4, 140.8 (q, $J = 38.4$ Hz), 137.2, 121.0 (q, $J = 268.4$ Hz), 97.6, 82.4, 35.9, 28.1.
6
7
8
9
10
11
12
13
14 ^{19}F NMR (376 MHz, Chloroform- d) δ -63.2. LCMS, positive mode, m/z : 266 $[\text{M}+\text{H}]^+$. Anal.
15
16
17 calcd. for $\text{C}_{10}\text{H}_{14}\text{F}_3\text{N}_3\text{O}_2$: C, 45.28; H, 5.32; N, 15.84. Found: C, 45.19; H, 5.37; N, 15.79.
18
19
20

21 *Tert-butyl (1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl)carbamate (14g).*

22
23
24 White powder. Yield = 54% (14.8 g). $R_f = 0.95$ (MTBE). ^1H NMR (500 MHz, Chloroform-
25 d) δ 8.49 (s, 1H), 6.91 (s, 1H), 3.89 (s, 3H), 1.50 (s, 9H). ^{13}C NMR (151 MHz, Chloroform-
26 d) δ 152.6, 146.8, 132.2 (q, $J = 39.2$ Hz), 119.6 (q, $J = 268.9$ Hz), 97.9 (q, $J = 2.8$ Hz),
27
28
29
30
31
32
33
34
35 81.0, 37.4 (d, $J = 1.8$ Hz), 28.2. ^{19}F NMR (470 MHz, Chloroform- d) δ -60.9. LCMS, positive
36
37
38 mode, m/z : 266 $[\text{M}+\text{H}]^+$. Anal. calcd. for $\text{C}_{10}\text{H}_{14}\text{F}_3\text{N}_3\text{O}_2$: C, 45.28; H, 5.32; N, 15.84.
39
40
41
42 Found: C, 45.54; H, 4.93; N, 16.12.
43
44

45 **Step 2.** The corresponding Boc-protected derivative **11g** or **14g** (26.5 g, 0.1 mol) was
46
47
48 dissolved in DCM (100 mL) and 10 M dry HCl in dioxane (50 mL) was added by one
49
50
51
52
53
54
55
56
57
58
59
60 collected by filtration and dried in vacuo (1 mm Hg, rt) affording corresponding amines as

1
2
3 partial hydrochlorides **11h** and **14h**, respectively. The residue was mixed with DCM – 30%
4
5
6
7 aq K₂CO₃ (1:2; 1 L) to the precipitate completely dissolved. The organic layer was
8
9
10 separated and the water layer was washed with DCM (3x100 mL) Then the combined
11
12
13 DCM phase was dried over Na₂SO₄ (100 g) and filtered through SiO₂. The solvent was
14
15
16 evaporated affording the desired compounds **11h** and **14h** as bases.
17
18
19

20
21 *1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-amine (11h).*
22

23
24 Orange crystalline powder. Yield = 83% (17.0 g). M.p. = 99 °C. ¹H NMR (400 MHz,
25
26 Chloroform-*d*) δ 5.78 (s, 1H), 3.72 (s, 2H), 3.69 (s, 3H). ¹³C NMR (126 MHz, Chloroform-*d*)
27
28 δ 145.4, 140.7 (q, *J* = 37.7 Hz), 121.3 (q, *J* = 268.1 Hz), 89.5 (q, *J* = 2.3 Hz), 34.8. ¹⁹F
29
30 NMR (376 MHz, Chloroform-*d*) δ -63.2. LCMS, positive mode, *m/z*: 166 [M+H]⁺. Anal.
31
32 calcd. for C₅H₆F₃N₃: C, 36.37; H, 3.66; N, 25.45. Found: C, 36.64; H, 3.62; N, 25.24.
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41
42 *1-Methyl-5-(trifluoromethyl)-1H-pyrazol-3-amine (14h).*
43

44
45 Pale brown crystalline powder powder. M.p. = 96-98 °C. Yield = 77% (15.9 g). ¹H NMR
46
47 (400 MHz, DMSO-*d*₆) δ 5.90 (s, 1H), 4.94 (s, 2H), 3.67 (s, 3H). ¹³C NMR (126 MHz,
48
49 DMSO-*d*₆) δ 154.9, 130.6 (q, *J* = 37.8 Hz), 120.5 (q, *J* = 268.6 Hz), 94.2, 37.2. ¹⁹F NMR
50
51 (376 MHz, DMSO-*d*₆) δ -59.7. EIMS, 70eV, *m/z* (rel. int.): 166 [M+H]⁺ (6); 165 [M]⁺ (100);
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3 164 (35); 146 (18); 122 (11); 117 (11); 52 (11). Anal. calcd. for C₅H₆F₃N₃: C, 36.37; H,
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6
7 3.66; N, 25.45. Found: C, 36.17; H, 3.38; N, 25.72.
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9

10 **The procedure of vapor pressure measurements.**

11
12
13
14 The values of the saturated vapor pressure of the compounds at different temperatures
15
16
17 were measured by the modified method of Ramsay and Young method, mercury
18
19
20 manometer was replaced by electronic. *Ca* 10 ml of each of the compounds was used for
21
22
23
24 vapor pressure measurements at various temperatures. The temperature was measured
25
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27
28 by a mercury thermometer located 1 cm above the boiling liquid. The vapor was
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32 continuously flown upon boiling on the thermometer. The measurement was performed
33
34
35
36 after the equilibrium set. For measurement of the vapor composition dependency on the
37
38
39 liquid composition *ca* 10 ml of the mixture of the compounds **1a** and **2a** with a known
40
41
42 molar ratio of two isomers was boiled and several drops of the distillate were collected,
43
44
45
46 the composition of the distillate was analyzed by ¹H and ¹⁹F NMR (the composition of the
47
48
49 initial mixture was also controlled by ¹H and ¹⁹F NMR). The results of ¹H and ¹⁹F NMR
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52
53 analyses were close and they were averaged. Then the experiment was repeated with
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57 another mixture of different composition. The instrument was thoroughly cleaned before
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3 the measurement of each of the points in order to eliminate residues of the compounds
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7 from the vials and condenser.
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10 11 12 13 ASSOCIATED CONTENT

14 15 16 17 Supporting Information

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20
21 The Supporting Information, which includes copies of ^1H , ^{13}C and ^{19}F NMR spectra of all
22
23
24 new compounds and CIF-file for compound **15d**, is available free of charge *via*
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26
27 www.pubs.acs.org (PDF).
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49 50 51 Notes

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53 The authors declare no competing financial interests.
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