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A Practical Synthetic Method for Functionalized 1-Methyl-3/5-(trifluoromethyl)-1*H*-pyrazoles

Maxim A. Tairov,[a] Vitalina Levchenko,[a] Ivan A. Stadniy,[a] Yurii V. Dmytriv,[a,b] Serhii O. Dehtiarov,[a] Mykola O. Kibalnyi,[a] Anton V. Melnyk,[a] Stanislav Y. Veselovych,[a] Yurii V. Borodulin,[a] Sergey V. Kolotilov,[c] Sergey V. Ryabukhin,[a,d] Dmitriy M.Volochnyuk*[a,d,e].*

[a] Enamine Ltd, 78 Chervonotkatska str., Kyiv, Ukraine

[b] National Technical University of Ukraine “Igor Sikorsky Kyiv Polytechnic Institute”, 37 Peremohy Ave., Kyiv, 03056, Ukraine

[c] L. V. Pisarzhevskii Institute of Physical Chemistry of the National Academy of Sciences of Ukraine, Prospekt Nauki 31, Kyiv, 03028, Ukraine

[d] Taras Shevchenko National University of Kyiv, 60 Volodymyrska str., Kyiv, Ukraine.

[e] Institute of Organic Chemistry, National Academy of Sciences of Ukraine, 5 Murmanska str., Kyiv, Ukraine.

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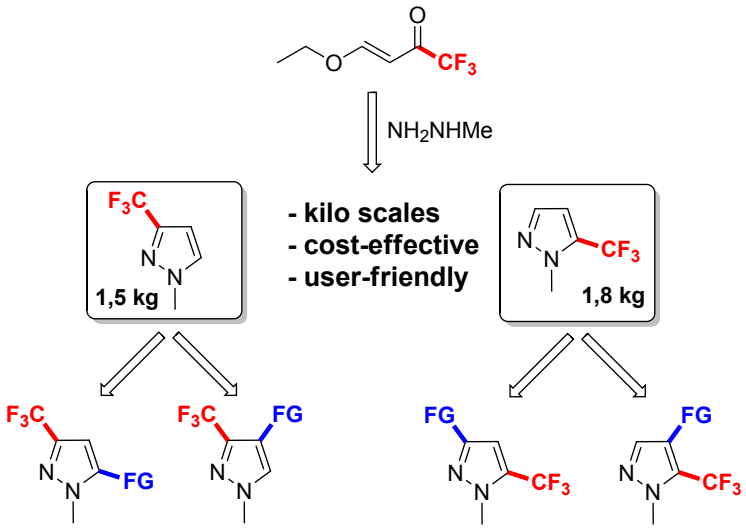


ABSTRACT. A new, high yielding and practical synthesis of 1-methyl-3-(trifluoromethyl)-1*H*-pyrazole and 1-methyl-5-(trifluoromethyl)-1*H*-pyrazole, key intermediates for important Medicinal and Agro Chemistry relevant building blocks, is developed. One step procedure for the regioisomeric mixture of target pyrazoles was proposed starting from 4-ethoxy-1,1,1-trifluoro-3-buten-2-one. The procedure for separation of this mixture was elaborated on the basis of the boiling point *vs*. pressure diagrams analysis. The efficient synthetic strategies to regioisomeric building blocks bearing CF_3-group at the 3-rd and the 5-th positions were demonstrated. A set of 1-methyl-3-(trifluoromethyl)-1*H*-pyrazoles containing such functional group as aldehyde, acid, boron pinacolate, lithium sulfinate and sulfonyl chloride was synthesized based on lithiation of 1-methyl-3-(trifluoromethyl)-1*H*-pyrazole in flow reactor. The bromination of both 1-methyl-3-(trifluoromethyl)-1*H*-

pyrazole and 1-methyl-5-(trifluoromethyl)-1*H*-pyrazole by NBS in mild conditions was performed. The introduction of the functional group into the 4-th position of 1-methyl-5-(trifluoromethyl)-1*H*-pyrazole was illustrated by the optimized synthesis of the corresponding aldehyde and acid based on Br-Li exchange in the appropriate bromide. Alternatively, the introduction of the functional group (acid and boron pinacolate) into the 5-th position of 1-methyl-5-(trifluoromethyl)-1*H*-pyrazole was performed based on DoM reaction of 4-bromo-1-methyl-5-(trifluoromethyl)pyrazole followed by catalytic reductive debromination.

KEYWORDS. trifluoromethyl pyrazoles, regioisomer separation, flow lithiation, bromine-lithium exchange, direct *ortho*-methalation, hydrogenative dehalogenation; building blocks.

INTRODUCTION

Pyrazole derivatives are the scaffolds of primary importance for medicinal,[1,2] agricultural,[3] supramolecular[4] chemistry as well as for materials sciences.[5,6] 3/5-Trifluoromethylpyrazoles, well-known examples of pyrazole derivatives, are key

privileged fragments, which are present in many agrochemicals and pharmaceuticals.[7,8] Among agrochemicals, herbicide Fluazolate (JV-485) **I**, used on winter wheat developed by Monsanto and Bayer AG, and fungicide Penthiopyrad **II**, developed by Mitsui Chemicals and DuPont, can be mentioned. Promising drug candidates ERDRP-00519 **III**, non-nucleoside inhibitor of the measles virus RNA-dependent RNA-polymerase,[9] and compound **IV**, interleukin-1 receptor-associated kinase inhibitor[10] can be highlighted (Figure 1). All these data clearly show that 3/5-trifluoromethylpyrazole fragments are playing an important role in different Agro and Medicinal Chemistry programs. Therefore, to continue our in-house program directed to the design and synthesis of fluorine-containing building blocks,[11] we desired to expand our stock by diverse functionalized 3/5-trifluoromethyl pyrazoles. Among innumerable possible variations of compounds with such core, the parent N-methyl-3/5-trifluoromethyl pyrazoles bearing the functional groups at the 4-th or the 3-d/5-th positions were chosen. These simplest derivatives are useful candidates in compound libraries design due to compliance with the “rule-of-two” (Ro2).[12] On the other side, for the generation of any preliminary SAR the introduction of regioisomeric simplest N-methyl substituent is desired.

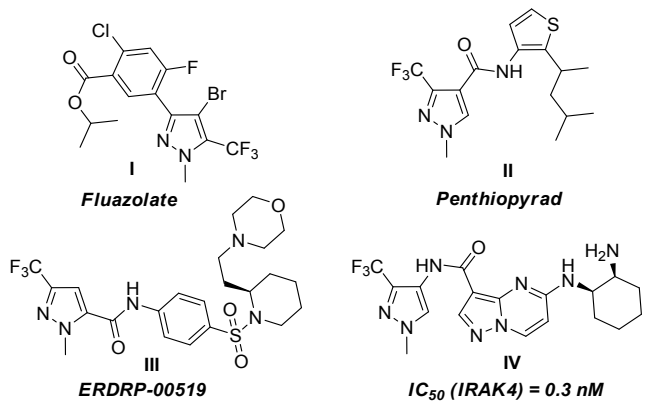
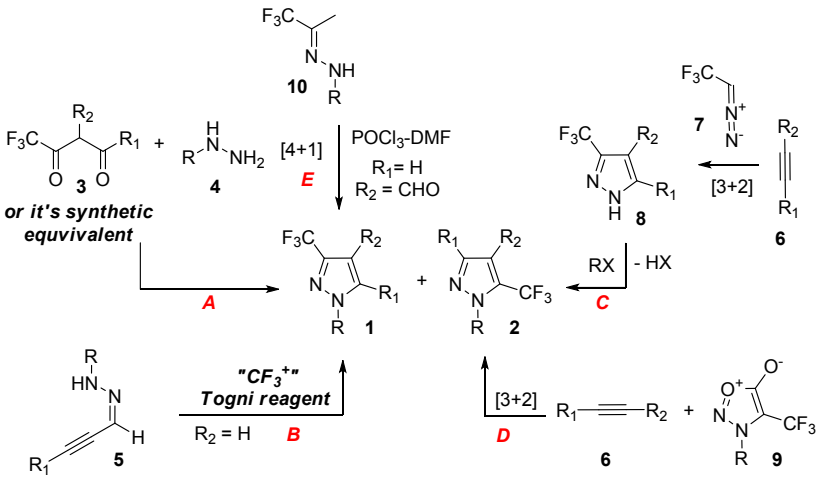


Figure 1. Examples of biologically active 1-methyl-3/5-(trifluoromethyl)-1*H*-pyrazoles.

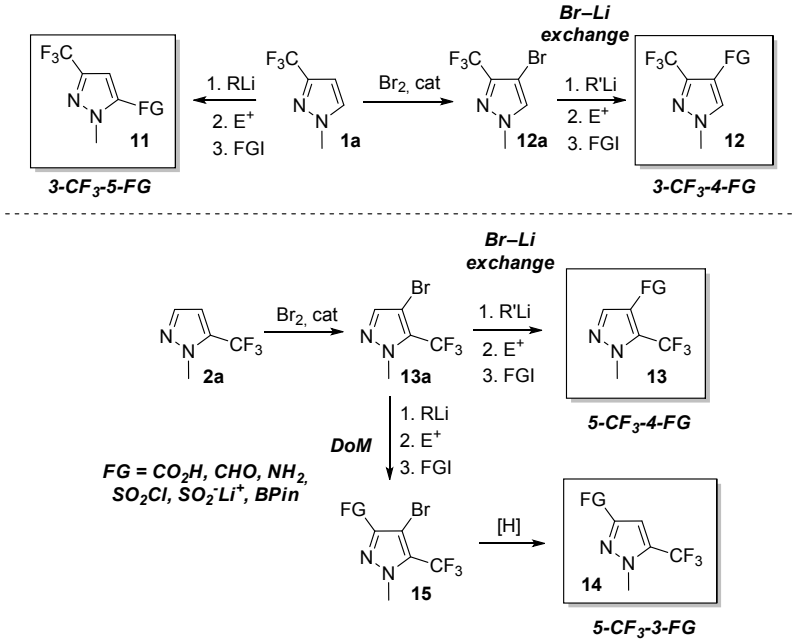
Despite the apparent simplicity, the selective synthesis of functionalized N-methyl pyrazoles is still a challenge. The traditional method for the synthesis of diverse functionalized 3/5-CF_3-substituted pyrazoles **1** and **2** is based on the cyclocondensation of 1,3-diketones **3** (or their synthetic 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

especially in the case of alkyl hydrazines. Moreover, $MeNHNH_2$ is the most inconvenient partner in such cyclocondensations due to the similar activity of the two nucleophilic centers. Alternatively the regioselective approach to 3-CF_3 pyrazoles **1** was developed on the basis of the electrophilic trifluoromethylation/cyclization of α,β-alkynic hydrazones **5** with Togni reagent (***way B***).[15] This approach was not tested on hydrazones, derived from methylhydrazine. In addition, the cost of Togni reagent is still high for use on a large scale. Recently the [3+2] cycloaddition based on the reaction of alkynes **6** and *in situ* generated CF_3CHN_2 (**7**) affording the pyrazoles **8** was elaborated in our company (***way C***).[16] This approach was later adapted to flow chemistry[17] as well as for the late-stage functionalization.[18] However, further alkylation of the *N*-unsubstituted pyrazoles **10** proceeds unselectively and again leads to a hardly separable mixture of regioisomers **1** and **2**.[19] It should be noted that the regioselective [3+2] cycloaddition involving CF_3-containing sydnone **9**, which results in 5-CF_3 pyrazoles, was reported (***way D***).[20] The method was applied for the synthesis of N-methyl pyrazole derivatives but the scale-up remains to be complex. To the best of our knowledge, only one example of a kilo-scale synthesis of pyrazoles, using sydnones, was described.[21] Finally, the approach based on

[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 SF_4 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 (NH_2, CO_2H, SO_2Cl, CHO)[25] as

well as BPin derivatives and sulfinates[26] as partners for Pd-catalyzed cross-coupling reactions. The general strategy chosen in this work is depicted on Scheme 2. For the synthesis of the *3-CF_3-5-FG* derivatives **11**, the next sequence was studied: the lithiation at the 5-th position / electrophilic substitution / functional group interconversion of 1-methyl-3-(trifluoromethyl)-1*H*-pyrazole **1a**. For the introduction of the functional group in the 4-th position of pyrazole **1a** (the synthesis of *3-CF_3-4-FG* derivatives **12**) the electrophilic bromination/Br-Li exchange followed by functionalization was used. In the case of 5-CF_3 derivatives, the installation of function in both positions started with electrophilic bromination of **2a**. Then, in the case of *5-CF_3-4-FG* derivatives **13**, the Br-Li exchange followed by further functionalization was optimized. From the other side, for the synthesis of *5-CF_3-3-FG* building blocks **14**, the bromine atom was used as a directing group for the DoM functionalization. This atom was then removed by hydrogenation. We recently used a similar approach for the pyridine derivatives synthesis.[27]

RESULTS AND DISCUSSION

The first milestone for the fulfillment of the above-mentioned strategy was to develop the kilo scale access to key starting pyrazoles **1a** and **2a**. Unfortunately, previous works,

including the seminal Schlosser's paper,[24] in which a possible selective synthesis of both isomers of 1-methyl-5/3-(trifluoromethyl)-1*H*-pyrazoles from 4-ethoxy-1,1,1-trifluoro-3-buten-2-one **16** and $MeNHNH_2$ in different condition was postulated,[28] was not reproduced in multi-gram scale. In all cases, the mixtures of both regioisomers were formed with different ratios. Therefore, we decided to elaborate a robust protocol for their separation. Due to the low molecular weight (150 Da) we expected that the isomers could be separated by distillation.[29] The boiling point *vs*. pressure diagram was measured for both regioisomers. It was found, that at 1 atm the difference of the boiling points for the isomers was *ca* 50 °C (90 and 140 °C), which was very promising for the successful separation (Figure 2). The measurement of the temperature-composition diagram at 1 atm for the mixture of compounds proved this assumption because, at a molar fraction of 1-methyl-3-(trifluoromethyl)-pyrazole (**1a**) from 0 to ca 0.75 in the liquid phase, the molar fraction of 1-methyl-5-(trifluoromethyl)-pyrazole (**1b**) in the gas phase exceeded 0.95 (Figure 3).

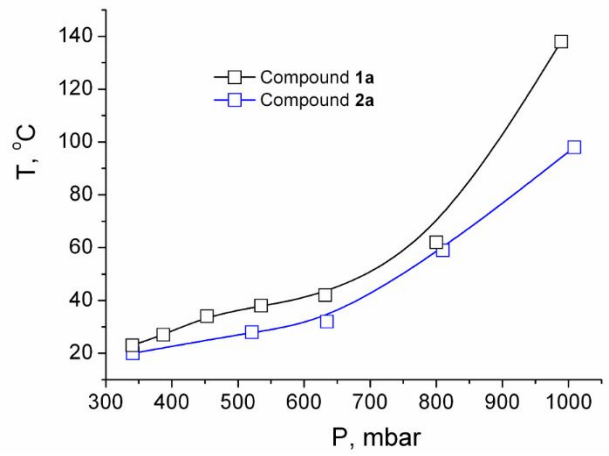


Figure 2. The boiling point–pressure diagram for compounds **1a** and **2a**.

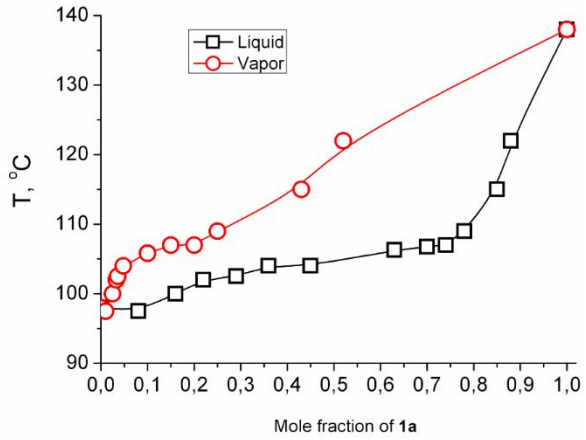
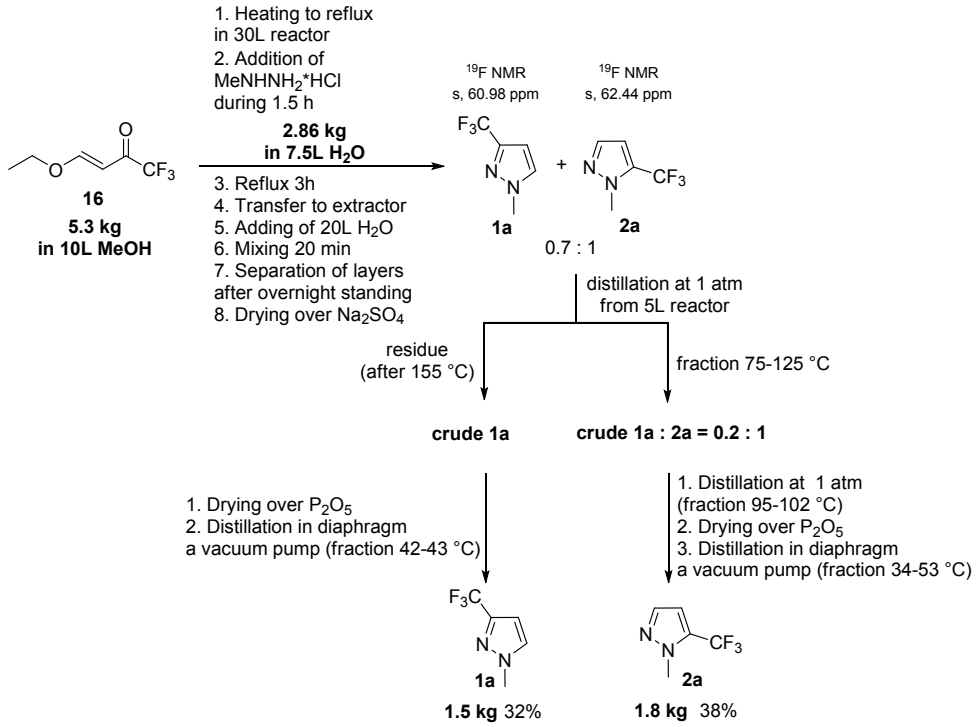


Figure 3. The temperature - composition diagram for the mixture of compounds **1a** and **2a** at 1 atm pressure.

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 $MeNHNH_2$ hydrochloride in the refluxed

MeOH-H_2O mixture (at 1:0.75 volume ratio) affording the mixture of regioisomeric pyrazoles **1a** and **2a** in 0.7:1 ratio according to the ^{19}F NMR spectra. The solubility of these two isomeric compounds in water is limited. Therefore, the addition of the excess of water to the reaction mixture leads to biphasic system formation, which could be easily separated. On this step, such impurities as unreacted methylhydrazine hydrochloride and HCl formed are also eliminated. The first fractional distillation of the crude mixture at 55–155 °C and atmospheric pressure gave several fractions, wherein the distillation residue contained only crude **1a**. The fraction boiling at 55–75 °C includes methanol, ethanol and a small amount of **2a**. The next fraction (75–125 °C) was the main one and contained the regioisomeric mixture of pyrazoles enriched by **2a** (0.2:1 isomers ratio). And the last fraction (125–155 °C) was the regioisomeric mixture of pyrazoles **1a** and **2a** in 1:1 ratio. The mass ratio between the main and other fractions was ca. 8:1. The further double re-distillation (the 1st at atmospheric pressure, the 2nd using diaphragm pump) of the main fraction enriched by an isomer **2a** led to the desired compound in 38% yield. It appeared to be reasonable to collect the last fraction from several synthetic runs and it also could be separated. The re-distillation of combined residues after the first distillation led to **1a**

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).



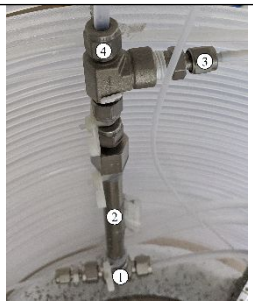
Scheme 3. Kilogram-Scale Process for the synthesis of 1-methyl-3-(trifluoromethyl)-1*H*-pyrazole and 1-methyl-5-(trifluoromethyl)-1*H*-pyrazole.

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-CF$_3$-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.

a) The general appearance of the flow system. 1) PFA flow spirals, mixers, temperature sensors for all stages inside a dry ice-cooled insulated IPA bath; 2) Temperature sensor connectors; 3) Liquid inlet/outlet connectors; 4) Stirred product collection bottle, under argon; 5) Reagent and wash solvent bottles, under argon; 6) Process controller (emergency pressure system shutoff and temperature sensors readouts); 7) Argon pressure regulator for reagent/product bottles; 8) Peristaltic pump bank, pressure sensors and reagent/wash selector valves.

b) Flow spirals. 1) 90 ml pre-cooling spiral; 2) 110 ml pre-cooling spiral; 3) 620 ml spiral; 4) 320 ml spiral.



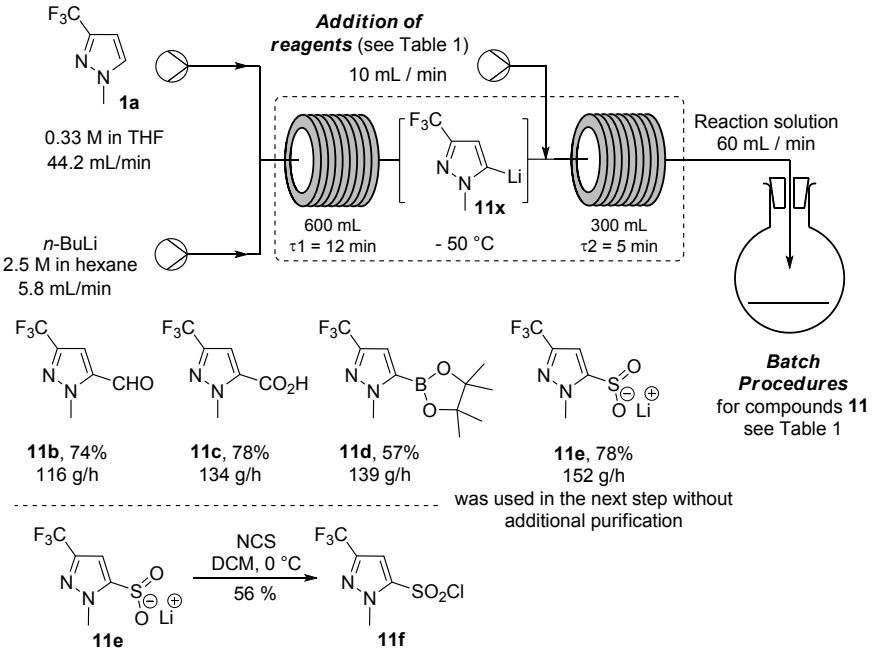
c) Example of the mixer (1 of 3). 1) tee piece, stainless steel; 2) static mixer, stainless steel; 3) Pt100 temperature sensor port; 4) outlet to spiral.

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

mL and 100 mL, respectively). More concentrated solutions of the compound **1a** in THF could not be used in our procedure due to the formation of precipitate during the flow process. It was found that the optimal temperature was –50 °C while the generation residence time was 12 min for the 600 mL reactor volume. The further treatment of the lithiated pyrazole **11x** was carried out in two different ways. In the case of synthesis of aldehyde **11b** and boronic ester derivative **11d** the solution of electrophilic reagent (1.5 eq of DMF or 1.2 eq. of *i*-PrOBPin, respectively) in THF was added via the third channel and further reaction started in the second 300 mL reactor with 5 min residence time at –50 °C. In the case of DMF, this 5 min time appeared to be sufficient for the reaction completion. The reaction mixture could be treated for further isolation/purification immediately giving the desired product **11b** in 74% yield. In the case of boronic ester derivative **11d** the reaction time 5 min at –50 °C was not sufficient for its completion. Therefore, in this case the collected reaction mixture was additionally maintained in a batch reactor at room temperature overnight before product isolation. The yield of the purified boronic ester derivative **11d** was 57%. In the case of acid **11c** and lithium pyrazolylsulfinate **11e**, the electrophilic reagents were gaseous. Therefore, for these

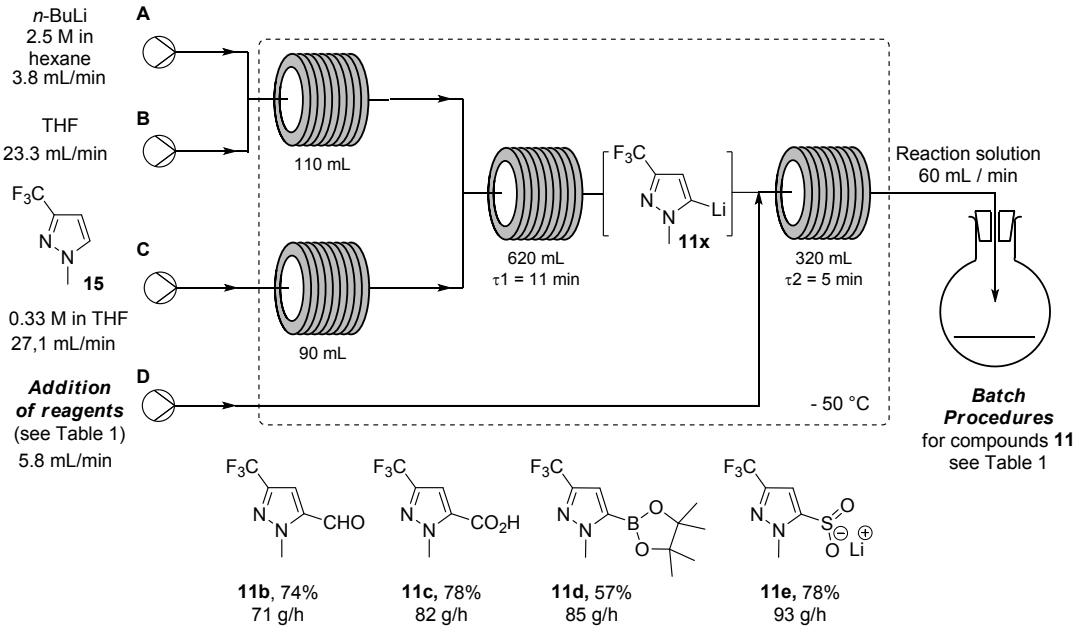
syntheses, another approach was used. To avoid the principal re-designing of flow system pure THF was added to the third channel and ca ~0.25 M solution of lithiated pyrazole **11x** in THF formed in the batch variant. For **11c** ~0.25 M solution of **11x** was collected into the reactor containing 2-fold excess of dry ice. After the reaction completion at room temperature and evaporation of the excess of CO_2 the desired acid **11c** was isolated in 78% yield. For the efficient synthesis of lithium pyrazolylsulfinate **11e**, the above-mentioned solution of organolithium **11x** was collected in the batch reactor cooled to –50 °C. The 5-fold excess of gaseous SO_2 was bubbled through this solution. Then the reaction mixture was kept at room temperature and the sulfinate **11e** precipitated in 78% yield. All these processes could be easily scaled up to kilo-scale. Even in the above-mentioned system the productivity of the processes was 116-152 g/h (Scheme 4, Table 1). Finally, the important building block – corresponding sulfonyl chloride **11f** – was obtained by batch chlorination of pyrazolylsulfinate **11e** by NCS in DCM at 0 °C in 56% yield affording more than 30 g of the compound in one synthetic run (Scheme 4).



Scheme 4. The synthesis of 5-functionalyzed 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-functionalyzed 1-methyl-3-(trifluoromethyl)-1*H*-pyrazoles (*3-CF$_3$-5-FG*) **11** (flow system **B**).

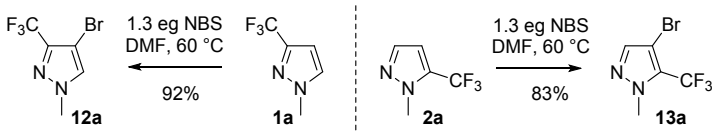
Table 1. Conditions for the flow synthesis of the compounds **11b-e**.

#	Cpd	FG	Additional reagent	Batch procedures	Yield, %	Productivity, g/h (A/B)
1	**11b**	CHO	2.2 M DMF in THF	1. Saturated NH_4Cl 2. Evaporation 3. MTBE-H_2O treatment 4 Organic phase evaporation 5. Chromatography SiO_2/hexane-MTBE (10:1, Rf = 0.9).	74	116 / 71
2	**11c**	CO_2H	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_2O. 4. The water phase was acidified by H_3PO_4 to pH = 2 and the precipitate formed was collected by filtration	78	134 / 82

3	**11d**	BPin	1.8 M *i*PrOBPin in THF	1. The reaction solution was collected and maintained overnight at rt. 2. Evaporation 3. MTBE-H_2O treatment 4 The organic phase was evaporated 5. Chromatography SiO_2/hexane-MTBE (85:15, Rf = 0.85)	57	139 / 85
4	**11e**	SO_2Li	pure THF	1. The reaction solution was collected in a batch cooled to -50 °C. 2. The flow of gaseous SO_2 was passed (5-fold excess) through a solution formed. 3. The solution was maintained overnight at rt. 4. The precipitate formed was collected by filtration and washed by MTBE	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 Br_2/Fe system at 100 °C was utilized.[24] When the 200 g of staring 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.

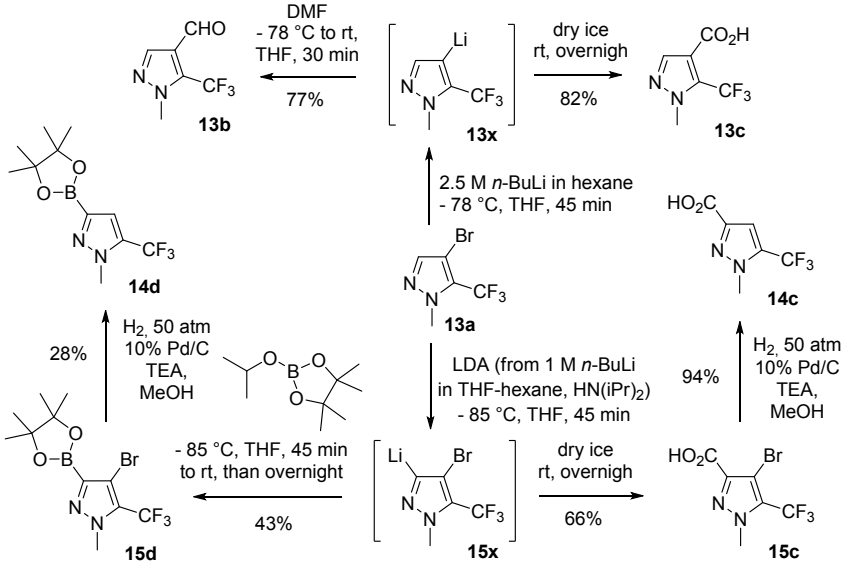
Among two brominated isomers, 4-bromo-5-CF_3 one was chosen for the further Br-Li exchange. In the case of 4-functionalized-3-CF_3 building blocks, the core starting material is the corresponding acid, which is now readily commercially available (according to SciFinder > 10 suppliers propose it in a 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 Et_2O at -75 °C.[24] The lack of such an approach was the use of both *t*-BuLi and Et_2O which was

not a convenient reagent/solvent combination for safe performance, especially in a large scale. We found that selective Br-Li exchange could be achieved by *n*-BuLi treatment in THF at -78 °C in a batch reactor. The adaptation of the protocol to the flow reactor failed due to precipitation of the LiBr from the reaction mixture. Generation of the corresponding lithium derivative **13x** was scaled up to 50g of starting bromide **13a** in 2L three-necked reactor. The subsequent reaction of this organolithium derivative **13x** with DMF or CO_2 afforded the aldehyde **13b** or corresponding acid **13c** in 77% and 82% yields, respectively (Scheme 7). These examples indicated the perspective of the approach to ***5-CF$_3$-4-FG*** derivatives in scale.

Starting from 4-bromo-1-methyl-5-(trifluoromethyl)pyrazole **13a** we also tested the multigram scale approach to ***5-CF$_3$-3-FG*** derivatives **14** based on DoM lithiation-functionalization-debromination (see Scheme 2). In seminal Schlosser paper, the DoM lithiation was performed by the reverse addition of the substrate to LDA solution in THF/hexane. We checked if the “normal” addition of LDA solution to the pyrazole **13a** could be performed. It was found, that the reaction proceeded cleanly but at the temperatures below -85 °C. The process requiring such low temperatures could not be

successfully adapted to flow mode. Using the flow reactor in the conditions typical for similar purposes (-70 °C to -30 °C, residence time on lithiation step from 5 to 20 min, and trapping residence from 2 to 10 min) led to the significant formation of the isomeric side product due to the "halogen dance" reaction.[31] As in the previous case with Br-Li exchange, the DoM generation of lithium derivative **15x** was scaled up to 50g of the starting bromide **13a** in 2L three-necked reactor but at -85 °C. The trapping of the organolithium derivative **15x** by dry ice afforded the corresponding acid **15c** in 66% preparative yield. Alternatively, compound **15x** was subjected to the reaction with iPrOBPin leading to the corresponding boronic acid pinacolate **15d** formation in 43% preparative yield. The structure of the boron derivative was unambiguously determined by the single-crystal X-ray diffraction study which proved the absence of the "halogen dance" reaction (Scheme 3, Figure 5). For the synthesis of parent ***5-CF_3-3-FG*** derivatives, we tested the debromination by catalytic hydrogenation over Pd/C catalyst. In the case of bromoacid **15c**, the hydrogenation proceeded cleanly at 50 atm in MeOH at the presence of triethylamine producing the desired product **14c** in 94% preparative yield on 30 g scale. 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.

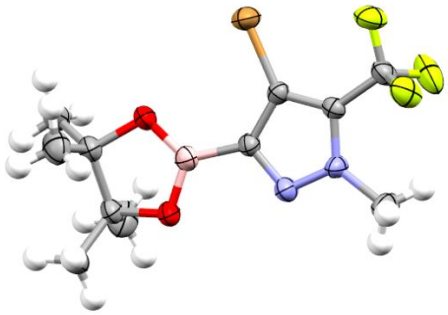
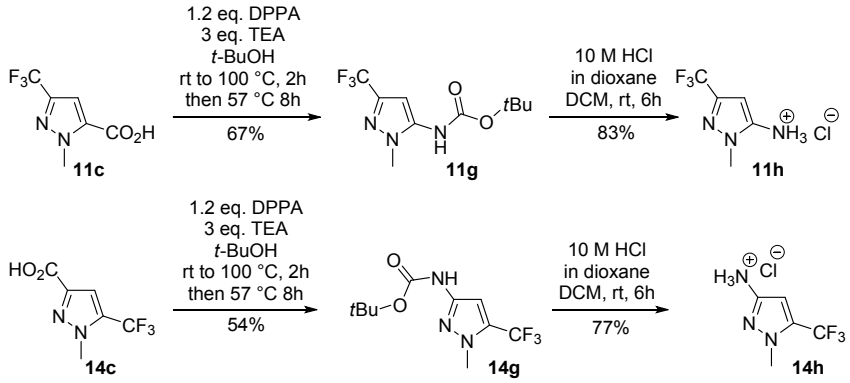


Figure 5. X-ray structure of compound **15d**.[32]

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

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



Scheme 8. Curtius-type rearrangement of pyrazolylcarboxylic acids.

CONCLUSION

In summary, an efficient and practical kilo-scale procedure for 1-methyl-3-(trifluoromethyl)-1*H*-pyrazole and 1-methyl-5-(trifluoromethyl)-1*H*-pyrazole was developed on the basis of cyclization of 4-ethoxy-1,1,1-trifluoro-3-buten-2-one with methylhydrazine hydrochloride with subsequent regioisomers separation by distillation. This protocol opens the door to the active use of these compounds as starting materials for the design and synthesis of important MedChem and AgroChem relevant building blocks. For the introduction of the functional group into the 5-th position of 1-methyl-3-(trifluoromethyl)-1*H*-pyrazole, the flow lithiation by n-BuLi was developed followed with trapping by the electrophilic reagent. The efficiency of the methodology was proven by the synthesis of corresponding examples of aldehyde, acid, boron pinacolate and lithium sulfinate in 57-78% yield and productivity 116-152 g/h. The batch mild conditions for the bromination of both 1-methyl-3-(trifluoromethyl)-1*H*-pyrazole and 1-methyl-5-(trifluoromethyl)-1*H*-pyrazole by NBS were developed and the synthesis was scaled up to 200 g in one synthetic run. The Br-Li exchange in 4-bromo-1-methyl-5-(trifluoromethyl)pyrazole was optimized, and a hazardous combination of t-BuLi in Et_2O was replaced by much more safe *n*-BuLi in THF. Based on the method, the corresponding

aldehyde and acid were synthesized in 50 g scale. Also, in the same scale, the direct ortho-metalation of the 4-bromo-1-methyl-5-(trifluoromethyl)pyrazole by LDA was developed for the synthesis of the corresponding acid and boron pinacolate. For the synthesis of "parent" 1-methyl-5-(trifluoromethyl)-1*H*-pyrazoles bearing function in the 3-rd position, the catalytic hydrogenative debromination of the DoM products was accomplished. Finally, the handy procedure for the Curtius-type rearrangement leading to amines was proposed.

EXPERIMENTAL SECTION

General. The solvents were purified according to the standard procedures. All starting materials were obtained from Enamine Ltd. Melting points were measured on automated melting point system. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 500 MHz for Protons and 126 MHz for Carbon-13) and Varian Unity Plus 400 spectrometer (at 400 MHz for protons, 101 MHz for Carbon-13, and 376 MHz for Fluorine-19). Tetramethylsilane (^{1}H, ^{13}C) or C_6F_6 (^{19}F) were used as

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 (±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 NH_2NH_2·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

separation. The organic phase was separated and dried over Na_2SO_4 overnight (100 g of sulfate for 1 kg of the desired product). This crude mixture (consisting of 3-CF_3 and 5-CF_3 isomers in 0.7:1 ratio) was transferred into the 5L round bottom distillation apparatus with 25 cm fractioning column, and fractioned at atmospheric pressure. Three fractions were collected: 55-75 °C, ca 200g (methanol, ethanol and small amount of 5-CF_3 isomer); 75-125 °C, 2.4 kg (5-CF_3 and 3-CF_3 isomers in 1:0.2 ratio); 125-155 °C, *ca* 300 g (3-CF_3 and 5-CF_3 isomers in 1:1 ratio). The residue after such distillation contained only raw 3-CF_3 isomer. This residue was distilled using the vacuum pump (Ilmvac Gardner Denver MPC 301 Zp, 230V 50/60Hz with the pressure down to 8 mbar) at 32-55 °C. The collector was cooled by the ice-ethanol mixture. The collected raw 3-CF_3 isomer was dried over P_2O_5 (20 g of oxide per 1 kg of the desired product) and re-distilled using the same vacuum pump at 42-43 °C affording pure compound **1a** as a colorless liquid (1.5 kg, 31.7%). The second fraction after the first distillation bearing the mixture of 3-CF_3 and 5-CF_3 isomers in 0.2:1 ratio was transferred into the 4L round bottom distillation apparatus with 25 cm fractioning column. Then it was distilled at atmospheric pressure keeping the bath temperature 135 °C. The collected fraction (2.0 kg) at 95-102 °C contained the raw 5-CF_3

isomer and the residue (~150g) was the crude mixture of 3-CF_3 and 5-CF_3 isomers in 1:1 ratio. The collected raw 3-CF_3 isomer was dried over P_2O_5 (20 g of oxide per 1 kg of the desired product) and distilled using the vacuum pump cited above at 34-35 °C. The obtained distillate was cooled by the ice-ethanol mixture affording pure compound **2a** as a colorless liquid (1.8 kg, 38.1%)

1-methyl-3-(trifluoromethyl)-1*H*-pyrazole (1a): colorless liquid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.37 (s, 1H), 6.48 (d, *J* = 2.3 Hz, 1H), 3.93 (s, 3H). ^{13}C NMR (126 MHz, 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. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -62.4. EIMS, 70eV, m/z (rel. int.): 151 $[M+H]^+$ (6); 150 $[M]^+$ (100); 149 (43); 131 (35); 129 (12); 81 (11); 69 (19); 54 (17); 52 (12); 42 (17). Anal. calcd. for $C_5H_5F_3N_2$: C, 40.01; H, 3.36; N, 18.66. Found: C, 39.63; H, 3.56; N, 18.56.

1-methyl-5-(trifluoromethyl)-1*H*-pyrazole (2a): colorless liquid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.61 (s, 1H), 6.86 (s, 1H), 3.96 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 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. ^{19}F NMR (376 MHz, DMSO-d_6) δ -59.5. EIMS, 70eV, m/z (rel. int.): 151 $[M+H]^+$ (7); 150 $[M]^+$

(100); 149 (41); 131 (34); 129 (12); 69 (12); 54 (12); 42 (12). Anal. calcd. for $C_5H_5F_3N_2$: C, 40.01; H, 3.36; N, 18.66. Found: C, 39.88; H, 3.09; N, 19.03.

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

Four pumps (Masterflex L/S peristaltic pumps with pump heads for PTFE tubing) were used to pump the solutions of the three reagents (see Scheme 5). The feedstock **A** was commercially available 2.5 M n-BuLi in hexane used directly from the supplied bottle and pumped at 3.8 mL/min. The feedstock **B** was THF (pumped at 23.3 mL/min to dilute feedstock **A** inflow). The feedstock **C** consisted of 1-methyl-5-(trifluoromethyl)-1*H*-pyrazole **1a** dissolved in anhydrous THF as a 0.33 M solution; it was pumped at 21.7 mL/min. The feedstock **D** contained different reagents (see Table 1) and pumped at 5.8 mL/min. All feedstocks were maintained under an atmosphere of argon. The reactors were fabricated from Altafluor 400 (PFA) tubing with an ID of 3/16 in a length of 34.6 m for the lithiation stage or the length of 17.3 m for the second stage. The residence time for the lithiation step was set to 12 min and the second step residence time was 5 min. Swagelok SS-400-3-4-TTF tees and Koflo1/4-40-3-12-2 static mixers (total internal volume 20 ml) were used. The pre-cooling loops (L = 5.2 m, ID = 3/16 in) and reactors for

both the lithiation and electrophilic reaction steps were submerged into a cooling bath set at -50 °C before initiating the three pumps. The temperature in the plug flow reactors was monitored and maintained at approximately -50 °C. After a steady flow was attained the product stream was collected and treated as indicated below.

*1-Methyl-3-(trifluoromethyl)-1H-pyrazole-5-carbaldehyde (**11b**).*

The feedstock **D** was 2.2 M DMF in THF. The collected product stream from the FC (after 4 h of system operation) process was quenched with saturated aq. NH_4Cl (600 mL). The solvent was evaporated in vacuo using a rotary evaporator. The residue was mixed with MTBE-water (3:1, 1.6 L) and extracted with MTBE (2x250mL). The organic phase was separated and washed with brine (5x300 mL) and dried over Na_2SO_4 (220 g). The solvents were evaporated and the residue was dissolved in n-hexane (300 mL) and passed through SiO_2 using 4L Schott filter funnel (L = 0.30 m, ID = 0.15 m) loaded with SiO_2 (1.7 kg) and *n*-hexane-MTBE, 10:1 as eluent (20 L) affording compound **11b** (R_f (*n*-hexane-MTBE, 10:1) = 0.9) as pale yellow liquid that crystallized over time (220 g, 74%).

Yellow crystalline powder. M.p. = 26-27 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.89 (s, 1H), 7.15 (s, 1H), 4.24 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 179.2, 141.7 (q,

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 MHz, Chloroform-*d*) δ -62.8. EIMS, 70eV, m/z (rel. int.): 179 $[M]^+$ (7); 178 $[M]^+$ (100); 177 (59); 159 (25); 149 (15); 81 (17); 80 (10); 69 (10); 52 (10). Anal. calcd. for $C_6H_5F_3N_2O$: C, 40.46; H, 2.83; N, 15.73. Found: C, 40.65; H, 2.99; N, 15.80.

*1-Methyl-3-(trifluoromethyl)-1H-pyrazole-5-carboxylic acid (**11c**).*

The feedstock **D** was pure THF. The product stream from the FC (after 4 h of system operation) process was collected into a batch reactor loaded with dry ice (1.5 kg) before initiating the three pumps. Then the reaction mixture obtained was maintained with stirring at rt 10h. The solvent was evaporated in vacuo using a rotary evaporator. The residue was mixed with DCM-water (1:4, 2 L) and extracted with DCM (2x350 mL). The water phase was separated and acidified by 85% aq. H_3PO_4 to pH = 2. The precipitate formed was collected by filtration and dried on air during 48 h affording the acid **11c** (HPLC purity 96.5%, 252 g, 78%).

Yellow crystalline powder. M.p. = 132 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 11.58 (br, 1H), 7.25 (s, 1H), 4.29 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 163.5, 141.2 (q, *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

MHz, Chloroform-*d*) δ -62.9. LCMS, negative mode, m/z: 193 $[M-H]^-$. Anal. calcd. for $C_6H_5F_3N_2O_2$: C, 37.13; H, 2.60; N, 14.43. Found: C, 37.08; H, 2.25; N, 14.53.

*1-Methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)-1H-pyrazole (**11d**).*

The feedstock **D** was 1.8 M iPrOBPin in THF. The collected product stream from the FC (after 4h of system operation) process was maintained with stirring at rt 10h and then quenched with saturated NH_4Cl (600 mL). The solvent was evaporated in vacuo using a rotary evaporator. The residue was mixed with MTBE-water (3:1, 1.6 L) and extracted with MTBE (2x250 mL). The organic phase was separated and washed with saturated aq $NaHCO_3$ (1x500 mL) and dried over Na_2SO_4 (220 g). Solvents was evaporated and the residue was dissolved in n-hexane (300 mL) and passed through SiO_2 using 4L Schott filter funnel (L = 0.30 m, ID = 0.15 m) loaded with SiO_2 (1.7 kg) and n-hexane-MTBE, 85:15 as eluent (15 L) affording compound **11d** with R_f = 0.85 as pale-yellow crystals (263 g, 57%).

Yellow crystalline powder. M.p. = 64-68 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.96 (s, 1H), 4.13 (s, 3H), 1.36 (s, 12H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 141.6 (q, *J* =

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 (376 MHz, Chloroform-*d*) δ -62.2. EIMS, 70eV, m/z (rel. int.): 277 $[M+H]^+$ (7); 276 $[M]^+$ (58); 275 (16); 262 (11); 261 (100); 260 (26); 257 (21); 233 (11); 219 (24); 191 (12); 190 (72); 177 (47); 176 (18); 165 (20); 157 (15); 85 (13); 59 (27); 58 (25); 57 (18); 43 (43); 42 (30); 41 (31); 39 (12). Anal. calcd. for $C_{11}H_{16}BF_3N_2O_2$: C, 47.86; H, 5.84; N, 10.15. Found: C, 47.99; H, 6.21; N, 9.96.

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

Feedstock **D** was pure THF. The product stream from the FC (after 4 h of system operation) process was collected in batch reactor cooled to -50 °C. The steam of gaseous SO_2 (5-fold excess, 267 g, 4.16 mol) was bubbled through this mixture from the damper camera. The reaction mixture was allowed to warm to rt and was maintained with stirring 10h. The precipitate formed was collected by filtration, washed with MTBE (3x200 mL) and dried in vacuo (1 mmHg, rt) affording sulfinate **11e** (HPLC purity 95.2%, 143 g, 78%).

White powder. M.p. = 267-274 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.45 (s, 1H), 3.96 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 160.2, 138.3 (q, *J* = 36.8 Hz), 122.3 (q, *J* = 268.1 Hz), 101.7 (q, *J* = 2.3 Hz), 38.0. ^{19}F NMR (376 MHz, DMSO-d_6) δ -60.5. LCMS,

negative mode, m/z: 213 $[M-Li]^-$. Anal. calcd. for $C_5H_4F_3LiN_2O_2S$: C, 27.29; H, 1.83; N, 12.73; S, 14.57. Found: C, 27.24; H, 1.56; N, 12.44; S, 14.35.

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

Sulfinate **11e** (50g, 0.23 mol) was suspended in dry DCM (1 L). NCS (33.4 g, 0.25 mol) was added to the stirred suspension by portions for 20 min at 0 ºC. The reaction mixture was stirred at rt 6h and then washed with water (3x250 mL) and saturated $NaHCO_3$ (3x350 mL) and dried over Na_2SO_4 (100 g). The solvent was evaporated and the residue was subjected to flash column chromatography over SiO_2 using *n*-hexane-MTBE 85:15 affording compound **11f** with R_f = 0.8 as a colorless liquid (31.7 g, 56%).

Colorless liquid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.27 (s, 1H), 4.30 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 142.5, 141.2 (q, *J* = 40.4 Hz), 119.8 (q, *J* = 269.6 Hz), 110.2 (q, *J* = 2.2 Hz), 39.9. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -63.0. LCMS, negative mode, m/z: 229 $[M-H_2O-H]^-$. Anal. calcd. for $C_5H_4ClF_3N_2O_2S$: C, 24.16; H, 1.62; N, 11.27; S, 12.90; Cl, 14.26. Found: C, 23.84; H, 1.71; N, 10.89; S, 13.12; Cl, 14.23.

*General protocol for the bromination of 1-methyl-3-(trifluoromethyl)-1H-pyrazole (**1a**) and 1-methyl-5-(trifluoromethyl)-1H-pyrazole (**2a**).*

The corresponding pyrazole (200.0 g, 1.33 mol) was mixed with DMF (1 L) in 4L round bottom reactor. Then NBS (296.5g, 1.66 mol) was added to the mixture. The mixture was heated to 60 ºC and stirred 10h. Then the mixture was cooled to rt and water was added (3 L). The solution formed was extracted with MTBE (3x0.7 L). The organic phase was separated, washed with brine (5x0.5 L) and saturated aqueous Na_2SO_3 (2x250 mL). The solvents were evaporated in vacuo and the residue was distilled using oil pump (2 mmHg) affording desired compounds as colorless liquids.

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

Yield = 92% (281.0 g). White crystalline powder. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.47 (s, 1H), 3.95 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 140.2 (q, *J* = 37.5 Hz), 132.7, 120.6 (q, *J* = 269.4 Hz), 91.5, 40.0. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -62.5. EIMS, 70eV, m/z (rel. int.): 230 $[M+H]^+$ (97); 229 $[M]^+$ (20); 228 (100); 227 (15); 211 (15); 209 (20); 69 (16); 42 (26). Anal. calcd. for $C_5H_4BrF_3N_2$: C, 26.22; H, 1.76; N, 12.23; Br, 34.89. Found: C, 26.59; H, 1.63; N, 11.95; Br, 34.86.

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

Yield = 83% (253.0 g). Colorless liquid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.48 (s, 1H), 4.02 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 140.2, 129.3 (q, *J* = 38.4 Hz), 119.8 (q, *J* = 270.1 Hz), 95.3, 39.7. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -59.1. EIMS, 70eV, m/z (rel. int.): 230 $[M+H]^+$ (97); 229 $[M]^+$ (33); 228 (100); 209 (11); 80 (12); 69 (22); 43 (11). Anal. calcd. for $C_5H_4BrF_3N_2$: C, 26.22; H, 1.76; N, 12.23; Br, 34.89. Found: C, 26.34; H, 1.79; N, 12.38; Br, 34.70.

*1-Methyl-5-(trifluoromethyl)-1H-pyrazole-4-carbaldehyde (**13b**).*

The 2L three-necked reactor was loaded with the solution of 4-bromo-1-methyl-3-(trifluoromethyl)-1*H*-pyrazole **13a** (50 g, 0.22 mol) in THF (500 mL) and 2.5 M n-BuLi in hexane (92 mL, 0.23 mol) was added dropwise at -78 ºC. The reaction mixture was maintained at -78 ºC during 45 min and the solution of DMF (23 mL, 0.3 mol) in THF (100 mL) was added dropwise at the same temperature. The mixture was maintained for 30 min and quenched with saturated NH_4Cl (300 mL). The solvent was evaporated in vacuo using a rotary evaporator. The residue was mixed with MTBE-water (4:1, 1.25 L) and extracted with MTBE (2x200 mL). The organic phase was separated and washed with brine (5x300 mL) and dried over Na_2SO_4 (180 g). The solvents were evaporated and the

residue was subjected to flash column chromatography over SiO_2 using n-hexane-MTBE 10:1 affording compound **13b** with R_f = 0.85 as white crystals (29.9 g, 74%).

White crystals. M.p. = 59 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.03 (s, 1H), 8.00 (s, 1H), 4.07 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 183.00 (q, *J* = 3.2 Hz), 139.3, 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). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -58.3. EIMS, 70eV, m/z (rel. int.): 178 $[M]^+$ (50); 177 (100). Anal. calcd. for $C_6H_5F_3N_2O$: C, 40.46; H, 2.83; N, 15.73. Found: C, 40.45; H, 3.09; N, 15.33.

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

The 2L three-necked reactor was loaded by solution of 4-bromo-1-methyl-3-(trifluoromethyl)-1*H*-pyrazole **13a** (50 g, 0.22 mol) in THF (500 mL) and 2.5 M n-BuLi in hexane (92 mL, 0.23 mol) was added dropwise at -78 ºC. The reaction mixture was maintained at -78 ºC for 45 min and then was poured on dry ice (96 g, 2.18 mol). Then the reaction mixture obtained was maintained for 10h with stirring at rt. The solvent was evaporated in vacuo using a rotary evaporator. The residue was mixed with DCM-water (1:4, 1.25 L) and extracted with DCM (2x250 mL). The water phase was separated and

acidified by 85% aq. H_3PO_4 to pH = 2. The precipitate formed was collected by filtration and dried on air during 48h affording acid **13c** (HPLC purity 97.3%, 34.7g, 82%).

Yellow powder. M.p. = 120 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.08 (s, 1H), 7.96 (s, 1H), 4.05 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.2, 141.5, 131.0 (q, J = 39.7 Hz), 120.0 (q, J = 270.4 Hz), 116.8, 40.8. ^{19}F NMR (376 MHz, DMSO-d_6) δ -56.5. LCMS, positive mode, m/z: 195 $[M+H]^+$. Anal. calcd. for $C_6H_5F_3N_2O_2$: C, 37.13; H, 2.60; N, 14.43. Found: C, 36.78; H, 2.80; N, 14.21.

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

The 2L three-necked reactor was loaded with the solution of 4-bromo-1-methyl-3-(trifluoromethyl)-1*H*-pyrazole **13a** (50 g, 0.22 mol) in THF (500 mL) and the solution of LDA (previously prepared from 2,5M n-BuLi in hexane (92 mL, 0.23 mol) and i-Pr_2NH (24.3 g, 0.24 mol) in THF (200 mL)) was added dropwise at -85 ºC. The reaction mixture was maintained at -85 ºC for 45 min and then was poured on dry ice (96 g, 2.18mol). Then the reaction mixture obtained was maintained for 10h with stirring at rt. The solvent was evaporated in vacuo using a rotary evaporator. The residue was mixed with DCM-water (1:3, 12 L) and extracted with DCM (2x250mL). The water phase was separated

and acidified by 85% aq. H_3PO_4 to pH = 2. The precipitate formed was collected by filtration and dried on air during 48h affording acid **15c** (HPLC purity 97.5 %, 39.6 g, 66%).

Yellow powder. M.p. = 144 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.44 (s, 1H), 4.07 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 161.5, 140.9, 130.7 (q, J = 37.4 Hz), 119.7 (q, J = 270.6 Hz), 97.8 (q, J = 2.2 Hz), 41.4 (q, J = 2.7 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ -58.2. LCMS, negative mode, m/z: 271 $[M-2H]^-$. Anal. calcd. for $C_6H_4BrF_3N_2O_2$: C, 26.40; H, 1.48; N, 10.26; Br, 29.27. Found: C, 26.41; H, 1.79; N, 9.94; Br, 29.31.

*4-Bromo-1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)-1H-pyrazole (**15d**).*

The 2L three-necked reactor was loaded with the solution of 4-bromo-1-methyl-3-(trifluoromethyl)-1*H*-pyrazole **13a** (50 g, 0.22 mol) in THF (500 mL) and the solution of LDA (previously prepared from 2,5M n-BuLi in hexane (92 mL, 0.23 mol) and i-Pr2NH (24.3 g, 0.24 mol) in THF (200 mL)) was added dropwise at -85 ºC. The reaction mixture was maintained at -85 ºC for 45 min and then the *i*PrOBPin was added dropwise at the same temperature. The mixture was maintained 30 min at -85 ºC and then 10h at rt and quenched with saturated NH_4Cl (250 mL). The solvent was evaporated in vacuo using a

rotary evaporator. The residue was mixed with MTBE-water (4:1, 1.25L) and extracted with MTBE (2x250 mL). The organic phase was separated and washed with saturated aq $NaHCO_3$ (2x400mL) and dried over Na_2SO_4 (180 g). The solvents were evaporated and the residue was subjected to column chromatography over SiO_2 using n-hexane-MTBE 85:15 affording compound **15d** with R_f = 0.85 as white crystals (33.2 g, 43%).

White crystalline powder. M.p. = 105 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.08 (t, *J* = 1.5 Hz, 3H), 1.38 (s, 12H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 143.2, 130.0 (q, *J* = 37.8 Hz), 119.9 (q, *J* = 270.3 Hz), 103.1, 84.5, 40.0 (q, *J* = 2.4 Hz), 24.8. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -58.9. EIMS, 70eV, m/z (rel. int.): 357 (9); 355 $[M]^+$ (96); 354 (73); 353 (88); 352 (91); 352 (19); 342 (10); 340 (94); 339 (100); 337 (20); 335 (20); 323 (45); 321 (43); 320 (12); 313 (62); 311 (64); 310 (16); 299 (14); 297 (17); 275 (48); 274 (14); 273 (11); 270 (15); 267 (15); 257 (78); 256 (49); 255 (90); 253 (46); 252 (12); 237 (10); 235 (12); 233 (48); 232 (14); 219 (10); 177 (13); 110 (24); 85 (62); 82 (54); 69 (21); 67 (39); 59 (31); 58 (15); 57 (25); 55 (13); 43 (73); 41 (66); 39 (25). Anal. calcd. for $C_{11}H_{15}BBrF_3N_2O_2$: C, 37.22; H, 4.26; N, 7.89; Br, 22.51. Found: C, 37.06; H, 4.38; N, 8.07; Br, 22.90.

*1-Methyl-5-(trifluoromethyl)-1H-pyrazole-3-carboxylic acid (**14c**).*

The 3L autoclave equipped with mechanical stirring was loaded with the solution of bromo derivative **15c** (27.2 g, 0.1 mol) in MeOH (600 mL). TEA (28 mL, 0.2 mol) and 10% Pd/C (5.3 g, 5 mmol) was added to the mixture formed. The mixture was treated at 50 atm of hydrogen pressure at 20 ºC during 24h. The precipitate formed was filtered off. The solvent was evaporated in vacuo. The residue was mixed with DCM-water (3:1, 800 mL) and acidified with 2M aq. HCl to pH = 2. The solution was extracted with DCM (2x150 mL). The organic phase was separated, dried over Na_2SO_4 (100 g) and the solvent was evaporated in vacuo affording acid **14c** (HPLC purity 98.1%, 18.2 g, 94%).

Yellow powder. M.p. = 125 °C.^{1}H NMR (400 MHz, DMSO-d_6) δ 13.18 (s, 1H), 7.27 (s, 1H), 4.03 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 162.3, 143.2, 132.3 (q, J = 39.4 Hz), 119.8 (q, J = 269.0 Hz), 110.7 (q, J = 2.5 Hz), 39.3 (q, J = 1.8 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ -59.9. LCMS, negative mode, m/z: 193 $[M-H]^-$. Anal. calcd. for $C_6H_5F_3N_2O_2$: C, 37.13; H, 2.6; N, 14.43. Found: C, 37.18; H, 2.25; N, 14.22.

*1-Methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)-1H-pyrazole (**14d**).*

The 3L autoclave equipped with mechanical stirring was loaded with the solution of bromo derivative **14d** (35.5 g, 0.1 mol) in MeOH (600 mL). TEA (28 mL, 0.2 mol) and 10% Pd/C (5.3 g, 5 mmol) was added to the mixture formed. The mixture was treated at 50 atm of hydrogen pressure at 20ºC during 4h. The precipitate formed was filtered off. The solvents were evaporated in vacuo and the residue was mixed with DCM (400mL) and 10% aq citric acid (200 mL). The organic phase was separated and dried over Na_2SO_4 (120 g). The solvents were evaporated and the residue was subjected to column chromatography over SiO_2 using n-hexane-MTBE 4:1 affording compound **14d** with R_f = 0.8 as a pale-yellow liquid that crystallized over time (7.7 g, 28%).

Yellow crystals. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.71 (s, 1H), 4.02 (s, 3H), 1.32 (s, 12H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 144.9, 135.7 (q, *J* = 39.6 Hz), 120.4 (q, *J* = 270.1 Hz), 100.7, 83.8, 38.5 (q, *J* = 2.7 Hz), 24.7. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -58.6. LCMS, positive mode, m/z: 277 $[M+H]^+$. Anal. calcd. for $C_{11}H_{16}BF_3N_2O_2$: C, 47.86; H, 5.84; N, 10.15. Found: C, 48.00; H, 5.74; N, 9.86.

General protocol for the Curtius-type rearrangement of pyrazolylcarbonic acids.

Step 1. The corresponding acid **11c** or **14c** (19.4 g, 0.1 mol) was dissolved in *t*-BuOH (200 mL) in the 1L round bottom reactor and TEA (41.8 mL, 0.3 mol) was added. DPPA (26 mL, 0.12 mol) was dropwise slowly added to the stirred mixture. The reaction mixture was very slowly heated to 100 ºC (during 2-3 h) on an oil bath to observe the gas evolution. **CAUTION**! Take care of the intensity of gas evolution. It should be stable and not very intense. When the temperature reached 100 ºC, the reaction mixture was maintained at for 1 additional hour. Then the mixture was cooled to room temperature and the solvent was evaporated in vacuo. The residue was mixed with MTBE – 30% aq K_2CO_3 (1:2; 1.2 L) and the precipitate formed was filtered off. This manipulation was repeated 3 times. Then the combined water phase was separated and extracted with MTBE (3x200 mL). The organic phase was separated and washed with water (3x250 mL) and dried over Na_2SO_4 (120 g). The solvent was evaporated and the residue was subjected to column chromatography over SiO_2 using MTBE as eluent affording the desired compounds **11g** and **14g**. The obtained compounds can be used in the next step without additional purification.

*Tert-butyl (1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)carbamate (**11g**).*

White powder. Yield = 67% (18.3 g). R_f = 0.95 (MTBE). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.70 (br, 1H), 6.39 (s, 1H), 3.75 (s, 3H), 1.48 (s, 9H). ^{13}C NMR (151 MHz, Chloroform-*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. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -63.2. LCMS, positive mode, m/z: 266 $[M+H]^+$. Anal. calcd. for $C_{10}H_{14}F_3N_3O_2$: C, 45.28; H, 5.32; N, 15.84. Found: C, 45.19; H, 5.37; N, 15.79.

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

White powder. Yield = 54% (14.8 g). R_f = 0.95 (MTBE). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.49 (s, 1H), 6.91 (s, 1H), 3.89 (s, 3H), 1.50 (s, 9H). ^{13}C NMR (151 MHz, Chloroform-*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), 81.0, 37.4 (d, *J* = 1.8 Hz), 28.2. ^{19}F NMR (470 MHz, Chloroform-*d*) δ -60.9. LCMS, positive mode, m/z: 266 $[M+H]^+$. Anal. calcd. for $C_{10}H_{14}F_3N_3O_2$: C, 45.28; H, 5.32; N, 15.84. Found: C, 45.54; H, 4.93; N, 16.12.

Step 2. The corresponding Boc-protected derivative **11g** or **14g** (26.5 g, 0.1 mol) was dissolved in DCM (100 mL) and 10 M dry HCl in dioxane (50 mL) was added by one portion at rt. The reaction mixture was stirred at rt 6h. The precipitate formed was collected by filtration and dried in vacuo (1 mm Hg, rt) affording corresponding amines as

partial hydrochlorides **11h** and **14h**, respectively. The residue was mixed with DCM – 30% aq K_2CO_3 (1:2; 1 L) to the precipitate completely dissolved. The organic layer was separated and the water layer was washed with DCM (3x100 mL) Then the combined DCM phase was dried over Na_2SO_4 (100 g) and filtered through SiO_2. The solvent was evaporated affording the desired compounds **11h** and **14h** as bases.

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

Orange crystalline powder. Yield = 83% (17.0 g). M.p. = 99 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.78 (s, 1H), 3.72 (s, 2H), 3.69 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) 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. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -63.2. LCMS, positive mode, m/z: 166 $[M+H]^+$. Anal. calcd. for $C_5H_6F_3N_3$: C, 36.37; H, 3.66; N, 25.45. Found: C, 36.64; H, 3.62; N, 25.24.

*1-Methyl-5-(trifluoromethyl)-1H-pyrazol-3-amine (**14h**).*

Pale brown crystalline powder powder. M.p. = 96-98 °C. Yield = 77% (15.9 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.90 (s, 1H), 4.94 (s, 2H), 3.67 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 154.9, 130.6 (q, *J* = 37.8 Hz), 120.5 (q, *J* = 268.6 Hz), 94.2, 37.2. ^{19}F NMR (376 MHz, DMSO-d_6) δ -59.7. EIMS, 70eV, m/z (rel. int.): 166 $[M+H]^+$ (6); 165 $[M]^+$ (100);

164 (35); 146 (18); 122 (11); 117 (11); 52 (11). Anal. calcd. for $C_5H_6F_3N_3$: C, 36.37; H, 3.66; N, 25.45. Found: C, 36.17; H, 3.38; N, 25.72.

The procedure of vapor pressure measurements.

The values of the saturated vapor pressure of the compounds at different temperatures were measured by the modified method of Ramsay and Young method, mercury manometer was replaced by electronic. *Ca* 10 ml of each of the compounds was used for vapor pressure measurements at various temperatures. The temperature was measured by a mercury thermometer located 1 cm above the boiling liquid. The vapor was continuously flown upon boiling on the thermometer. The measurement was performed after the equilibrium set. For measurement of the vapor composition dependency on the liquid composition *ca* 10 ml of the mixture of the compounds **1a** and **2a** with a known molar ratio of two isomers was boiled and several drops of the distillate were collected, the composition of the distillate was analyzed by ^{1}H and ^{19}F NMR (the composition of the initial mixture was also controlled by ^{1}H and ^{19}F NMR). The results of ^{1}H and ^{19}F NMR analyses were close and they were averaged. Then the experiment was repeated with another mixture of different composition. The instrument was thoroughly cleaned before

the measurement of each of the points in order to eliminate residues of the compounds from the vials and condenser.

ASSOCIATED CONTENT

Supporting Information

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

AUTHOR INFORMATION

Corresponding Authors

Sergey V. Ryabukhin s.v.ryabukhin@gmail.com ORCID: 0000-0003-4281-8268.

Dmitriy M. Volochnyuk d.volochnyuk@gmail.com ORCID: 0000-0001-6519-1467.

Notes

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(32) Crystallographic data for **15d** have been deposited with the Cambridge Crystallographic Data Centre, 11 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk). The deposition number is CCDC-2011680.