Organic & Biomolecular Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

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View Article Online
DOI: 10.1039/C7OB02373A

Journal Name

ARTICLE

Synthesis of 4-Subsituted Pyrazole-3,5-diamines via Suzuki-Miyaura Coupling and Iron-Catalyzed Reduction

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Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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The general and efficient synthesis of the 4-substituted-1*H*-pyrazole-3,5-diamines was develop to access the derivatives with an aryl, heteroaryl, or styryl group, which are otherwise relatively difficult to prepare. The first step is based on the Suzuki-Miyaura cross-coupling reaction utilizing the XPhos Pd G2 precatalyst. The coupling reactions of 4-bromo-3,5-dinitro-1*H*-pyrazole with the electron-rich/deficient or sterically demanding boronic acids enabled to give the corresponding dinitropyrazoles. Subsequent iron-catalyzed reduction of the both nitro groups with hydrazine hydrate accomplished the synthesis. The additional demethylation of the 4-methoxystyryl derivative allowed to provide the carboanalog of CAN508 reported as a selective CDK9 inhibitor.

Introduction

The compounds with a 1*H*-pyrazole-3,5-diamine moiety have been often involved in the biological studies focused on the antibacterial or antiviral activity.[1, 2] This moiety has also been used in the studies associated with the cell growth disorders to find efficient inhibitors of Caspase-3,[3] JAK2,[4] and cyclin-dependent kinase (CDK) proteins, which can be potentially exploited as drugs for cancer therapy.[5]

Previously, we reported novel 4-arylazo-3,5-diamino-1*H*-pyrazoles as potent and selective CDK inhibitors, where CAN508 was identified as the first known selective CDK9 inhibitor (Figure 1).[6, 7] The presence of the azo group in CAN508 can be potentially a subject of metabolic reduction since there is a well-known example described at the first sulfonamide drug, Prontosil.[8]

The metabolic lability of the azo group can be solved by its substitution with a vinyl moiety resulting in carboanalog **1** (Scheme 1). A suitable precursor, styrylpyrazole **4**, was reported by Shevelev using Knoevenagel condensation to form the styryl moiety from an activated 4-methylpyrazole and *p*-anisaldehyde. However, this method afforded unsatisfactory yields and a limited reaction scope was demonstrated.[9]

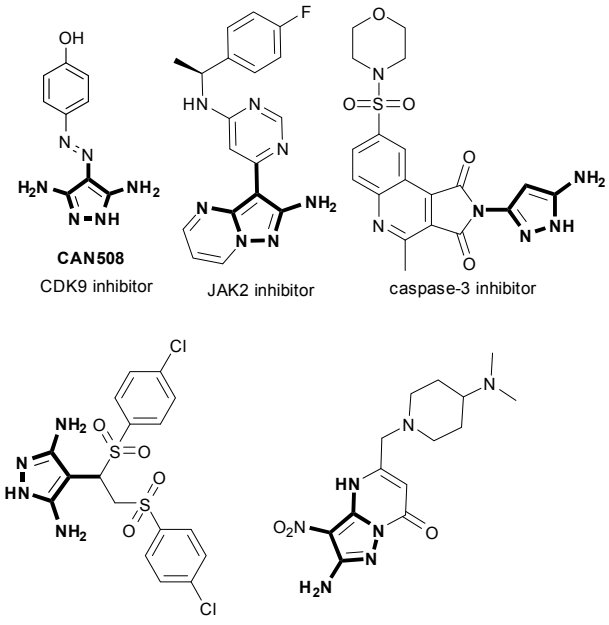

Figure 1. Examples of biological active compounds with 1*H*-pyrazole-3,5-diamine moiety.

An immediate precursor, pyrazole **5**, and its derivatives have not been described yet. Despite the cyclization of mono(hetero)aryl malononitriles with hydrazine hydrate seems at the first glance very simple to provide the 4-substituted-1*H*-pyrazole-3,5-diamines, the yields can be lowered by the competitive reactions revealed by Hartke[10] and

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Electronic Supplementary Information (ESI) available: See DOI: 10.1039/x0xx00000x

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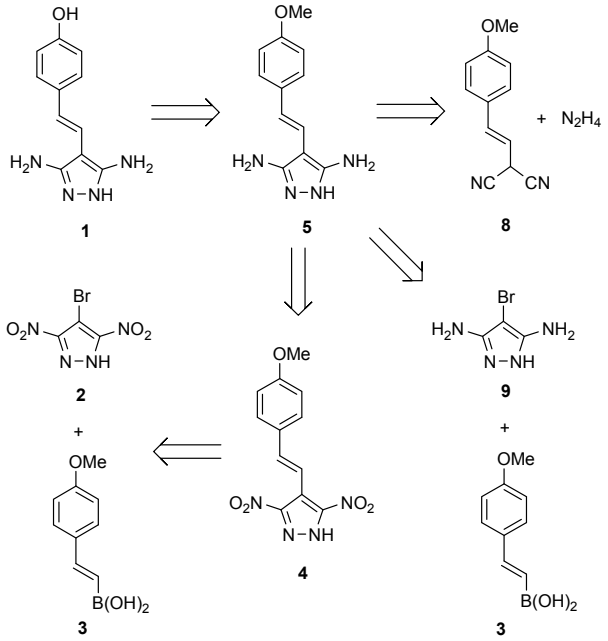
DOI: 10.1039/C7OB02373A

Sato.[11] More complicated side reactions can occur with styrylmalononitrile **8** or similar compounds.

Another possible access to **1** can be utilization of the Suzuki-Miyaura cross-coupling reaction (SMC) to join styryl **3** and pyrazole **2**. Since the SMC reaction is compatible with many functional groups and structural patterns, this strategy would offer to synthesize not only pyrazole **1**, but also a broad spectrum of diversely 4-substituted-1*H*-pyrazole-3,5-diamines after reduction.



Scheme 1. Retrosynthetic analysis of carboanalog **1**.

Despite the SMC reaction has been widely explored, there are still encountered limits, predominantly, when the heterocyclic systems are used as coupling partners.[12-14] These synthetic limits have obvious implications in drug development, since many biologically active compounds are frequently comprised of the nitrogen-containing heterocyclic moieties.[15, 16]

Generally, heterocyclic systems, especially N-azoles, are considered as challenging substrates with regard to their increased coordination susceptibility to a catalyst which usually leads to a decreased rate or complete inhibition of a cross-coupling reaction.[17-20] Further, the peripheral substitution of heterocyclic moieties with the functional groups possessing a Lewis base character can more complicate a cross-coupling reaction, especially substitution in ortho position to a reaction center.[21-Error! Reference source not found.24] Coordination activity of reactants and/or products can be overcome by utilization of protecting groups,[25-27] higher amount of a catalyst, higher temperature, and/or prolonged reaction time.[17, 28] Consequently, these factors have influence on the stability of coupling partners and we can observe common side reactions such as homocoupling, dehalogenation, and/or protodeboronation.[29, 30] To avoid these obstacles, the first choice is usually optimization of a (pre)catalyst, use of boronic acid esters, and/or higher amounts of reactants.

In the context of our research focused on the synthesis of CDK inhibitors we have identified the 3,5-diamino-1*H*-pyrazole moiety as an important pharmacophore binding to the CDK hinge region. A cross-coupling reaction of styrylboronic acid directly with bromopyrazole **9** can be potentially burden with side reactions originating from a lower stability of styrylboronic acid,[31] a significant coordination activity of the both amino groups, a possible formation of pyrazole-bridged Pd complexes,[17, 32] and a dehalogenation process.

We hypothesized that introduction of the electron-withdrawing nitro groups as a masked functionality for the both amino groups resulting in pyrazole **2** should improve the reactivity, despite the presence of the challenging factors representing the unprotected pyrazole endocyclic NH group and two sterically demanding *ortho*-positioned nitro groups. Good yields should be provided due to a lower coordination activity of a substrate/product, a decreased formation of the dimeric complexes, a significantly higher rate of the oxidative addition step, and a diminished dehalogenation side reaction, which we previously reported on the similar pyrazole derivative independent on the Pd species.[21, 29]

Herein, we report the development and the scope of a general and efficient catalytic system for the SMC reaction of dinitropyrazole **2** with the aryl-, heteroaryl-, or styrylboronic acids to give dinitropyrazoles **4** and their subsequent practical iron-catalyzed reduction into the desired diaminopyrazoles **5**.

Results and discussion

Our study started with the synthesis of dinitropyrazole **2**. 1*H*-Pyrazole was firstly brominated with NBS according to the reported procedure[33] and then resulting 4-bromo-1*H*-pyrazole was nitrated in a mixture of concentrated nitric and sulfuric acids. Subsequently, dinitropyrazole **2** was treated under microwave irradiation at 100 °C for 20 min with potassium phosphate, carbonate, and hydroxide to evaluate a possible Pd-independent dehalogenation side reaction. No dehalogenation occurred with phosphate, but dehalogenated pyrazole **6** was detected as a trace (1%) with carbonate, and hydroxide provided 14% of **6**. A markedly lesser degree of dehalogenation (hydroxide) or its complete suppression (phosphate) in comparison with the previously studied aminopyrazoles[29] can be attributed to the electron-withdrawing effect of the both nitro groups. We assume a formation of a more stable pyrazole anion during annular tautomerism, which diminishes a prototropic shift into a 4*H*-pyrazole tautomer and, concurrently, a Pd-independent reductive dehalogenation.

The optimization process of a catalytic system for pyrazole **2** was initiated at 100 °C with palladium acetate, potassium phosphate, and dioxane (Table 1, entries 1-6). While pyrazole **4a** was obtained in a very good yield with the XPhos ligand (82%), the SPhos ligand allowed only a fair yield (50%) as a consequence of a higher homocoupling side reaction rate resulting in biphenyl **7** and a lower conversion of bromopyrazole **2** (entries 3 and 4).

The APhos[38] ligand (entry 5), which was previously also utilized for the pyrazolyl bromides, afforded a good yield (76%). Comparable results were observed with the BINAP[39] ligand (entry 6). A classical

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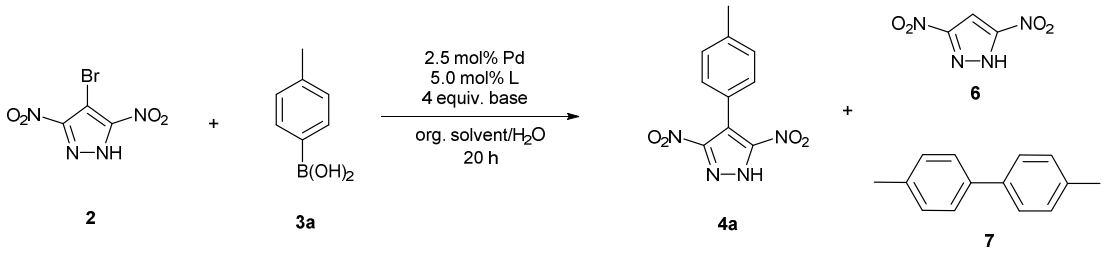
ligand, triphenylphospine, also provided good yields and, moreover, dehalogenated pyrazole **6** was not detected (entries 7 and 8).

Table 1. Optimization of reaction conditions.



entry	[Pd]	ligand	solvent	base	T (°C)	**4a**[b]	**2**[b]	**6**[b]	**7**[b]
1	$Pd(OAc)_2$	PCy_3	dioxane	K_3PO_4	100°C	25	39	4	24
2	$Pd(OAc)_2$	PAd_2Bu	dioxane	K_3PO_4	100°C	34	27	5	30
3	$Pd(OAc)_2$	XPhos	dioxane	K_3PO_4	100°C	82	3	2	11
4	$Pd(OAc)_2$	SPhos	dioxane	K_3PO_4	100°C	50	17	7	26
5	$Pd(OAc)_2$	APhos	dioxane	K_3PO_4	100°C	76	4	4	14
6	$Pd(OAc)_2$	BINAP	dioxane	K_3PO_4	100°C	74	6	2	8
7	$PdCl_2(Ph_3P)_2$	Ph_3P	dioxane	K_3PO_4	100°C	78	2	0	16
8	$Pd(Ph_3P)_4$	Ph_3P	dioxane	K_3PO_4	100°C	78	4	0	10
9	PEPPSI	PEPPSI	dioxane	K_3PO_4	100°C	7	63	1	22
10	**XPhos Pd G2**	**XPhos**	**dioxane**	**K_3PO_4**	**100°C**	**90**[c]	**>1**	**0**	**9**
11	XPhos Pd G2	XPhos	butanol	K_3PO_4	100°C	79	0	11	10
12	XPhos Pd G2	XPhos	DMF	K_3PO_4	100°C	86	>1	3	7
13	XPhos Pd G2	XPhos	toluene	K_3PO_4	100°C	42	27	2	24
14	XPhos Pd G2	XPhos	dioxane	K_2CO_3	100°C	80	2	>1	13
15	XPhos Pd G2	XPhos	dioxane	KOAc	100°C	3	40	>1	2
16	XPhos Pd G2	XPhos	dioxane	K_3PO_4	90°C	88[c]	1	1	7
17	XPhos Pd G2	XPhos	dioxane	K_3PO_4	80°C	82	5	0	8
18	XPhos Pd G2	XPhos	dioxane	K_3PO_4	60°C	74	6	>1	10
19	XPhos Pd G3	XPhos	dioxane	K_3PO_4	100°C	71	11	0	16
20	XPhos Pd G4	XPhos	dioxane	K_3PO_4	100°C	55	14	0	22

[a]Reaction condition: **2** (0.25 mmol), **3a** (0.262 mmol), organic solvent (1.0 mL), H_2O (0.25 mL), base (1.0 mmol), Pd-source (2.5 mol%), ligand (5.0 mol%), 20 h. [b]HPLC yield (%) determined from a crude reaction mixture with an inner standard (see Supporting Information for more details). [c]Reaction was carried out at a 1 mmol scale.

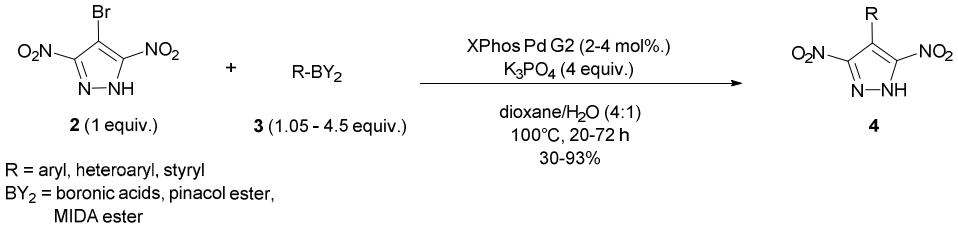
Carbene-based catalyst PEPPSI-IPr[40] gave unsatisfactory yield (entry 9). After the XPhos ligand was proved the best (entry 3), the evaluation of the isolation process at a 1 mmol scale pointed at difficulties associated with separation of starting bromopyrazole **2** from product **4a**. It was necessary to provide a complete conversion of **2** into **4a**. Gratifyingly, this issue was solved by the introduction of the precatalyst XPhos Pd G2, which allowed to give **4a** in the excellent yield (90%) due to a nearly complete conversion and eliminated dehalogenation side reaction (Table 1, entry 10).

Subsequent experiments confirmed the best reaction conditions described at entry 10. Substitution of dioxane with DMF or butanol provided a lower yield, which was further decreased when toluene was used (entries 11-13). Utilization of potassium carbonate instead of potassium phosphate did not improve the yield and potassium acetate was almost ineffective (entries 14-15). Gradual lowering of the reaction temperature led to decreased yields (entries 16-18). The third and fourth generation of the catalyst did not provide better yields, since the reaction has to be performed at 100 °C (entries 19-20).

DOI: 10.1039/C7OB02373A

With optimized conditions in hands (Table 1, entry 10), the scope of the SMC reaction of bis-ortho-substituted pyrazole **2** with various aryl, styryl, and heteroaryl boronic acids or MIDA esters was examined (Table 2).

Table 2. Scope of the Suzuki-Miyaura reaction using pyrazole **2**.



R = aryl, heteroaryl, styryl
BY_2 = boronic acids, pinacol ester, MIDA ester

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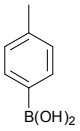
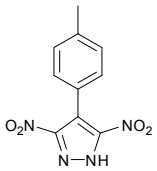
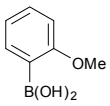
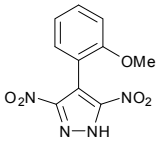
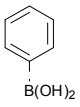
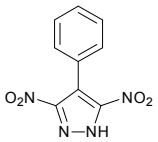
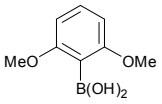
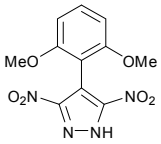
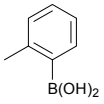
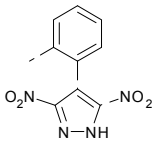
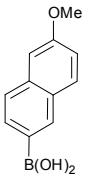
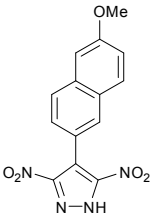
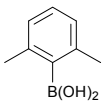
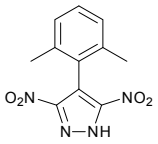
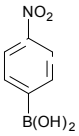
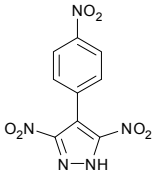
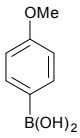
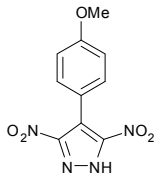
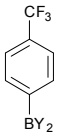
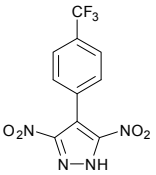
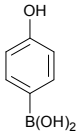
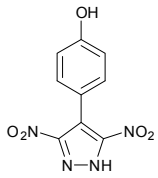
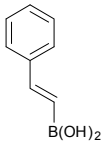
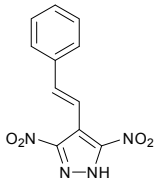
entry	boronic acid	time	product	entry	boronic acid	time	product
1	 **3a**	20 h	 **4a** (64%)	7	 **3g**	20 h	 **4g** (60%)
2	 **3b**	20 h	 **4b** (64%)[a]	8	 **3h**	48 h	 **4h** (84%)[b]
3	 **3c**	48 h	 **4c** (72%)[b]	9	 **3i**	20 h	 **4i** (65%)
4	 **3d**	48 h	 **4d** (no reaction)	10	 **3j**	48 h	 **4j** (75%)[b]
5	 **3e**	20 h	 **4e** (73%)	11	 **3k** A: **Y = OH** B: **Y = pin**	48 h	 **4k** A: (70%)[b] B: (93%)[b]
6	 **3f**	72 h	 **4f** (16%)[c]	12	 **3l**	20 h	 **4l** (62%)

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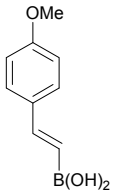
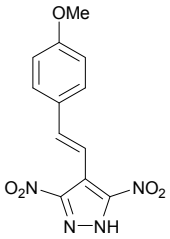
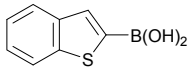
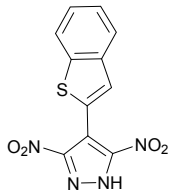
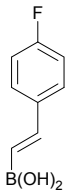
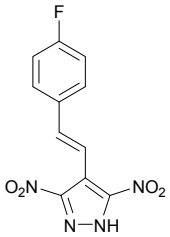
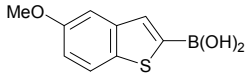
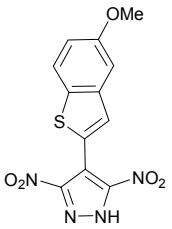
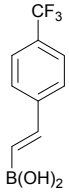
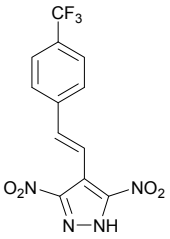
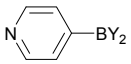
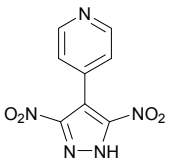
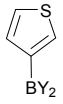
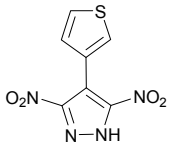
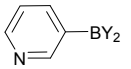
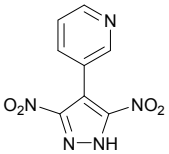
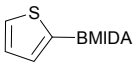
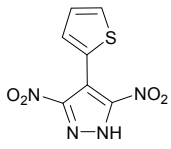
Table 2. Continued.

entry	boronic acid	time	product	entry	boronic acid	time	product
13	 **3m**	20 h	 **4m** (66%)	18	 **3r**	48 h	 **4r** (62%)[b]
14	 **3n**	20 h	 **4n** (80%)	19	 **3s**	48 h	 **4s** (70%)[e]
15	 **3o**	20 h	 **4o** (45%)	20	 **3t** A: **Y = OH** B: **Y = MIDA**	48h 48h	 **4t** A: (trace) B: (trace)
16	 **3p** A: **Y = OH** B: **Y = pin**	20 h	 **4p** A: (65%) B: (65%)	21	 **3u** A: **Y = MIDA** B: **Y = neopentylglycol ester**	72h 48h	 **4u** A = (trace) B = (trace)
17	 **3q**	48 h	 **4q** (30%)[d]				

[a]After 5 h addition of XPhos Pd G2 (2 mol%). [b]After 20 h addition of **3** (1.05 equiv.) and XPhos Pd (2 mol%). [c]Higher excess of **3f** (1.5 equiv.) was added, then after 20 h and 48 h additional amounts of **3f** (1.5 equiv.) and XPhos Pd G2 (2 mol%) were added; NMR yield. [d]After 20 h addition of **3q** (1.5 equiv.) and XPhos Pd G2 (2 mol%). [e]Higher excess of **3s** (1.5 equiv.) was added, then after 20 h additional amounts of **3s** (1.5 equiv.) and XPhos Pd G2 (2 mol%) were added.

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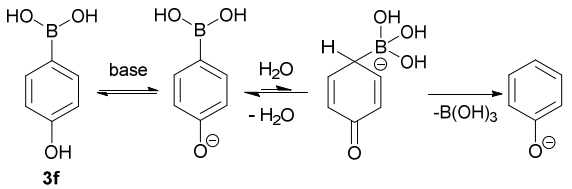
Pyrazoles **4a** and **4b** were isolated in fair yields (entries 1 and 2); however, an additional amount of the catalyst was necessary for **4b**. The reaction with *o*-tolylboronic acid afforded a slightly higher yield, but with the extra support of the catalyst and boronic acid **3c** (entry 3).

The considerably more sterically demanding bis-ortho-substitution led to the complete termination of the reaction (entry 4).

The electron-donating methoxy group at *para* position of boronic acid **3e** allowed the better yield in comparison to pyrazole **4a** (entry 5). The similar reaction was also attempted with boronic acid **3f** bearing unprotected OH group, but the yield was significantly lower (entry 6). A possible explanation of the unsatisfactory yield brought the LCMS analysis of a crude product. Two compounds difficult to separate with the identical molar mass were revealed. The NMR spectrum of this mixture confirmed the presence of the two compounds with the mono and para substituted benzene rings. It was hypothesized that boronic acid **3f** underwent a side protodeboronation reaction resulting in phenol and the subsequent Buchwald-Hartwig type coupling provided the isomeric phenoxy-substituted pyrazole. Our hypothesis was supported by the stability check of boronic acid **3f** under the same reaction conditions without the presence of the XPhos Pd G2 precatalyst and pyrazole **2**, which confirmed the complete protodeboronation into phenol within 2 hours. Further, the independent reaction of pyrazole **2** only with phenol provided the identical compound observed in the mixture of the two isomers after the coupling of pyrazole **2** with boronic acid **3f** (see Supporting Information).

Cheon proposed a protodeboronation mechanism based on a formation of an ate complex, where the C-B bond was cleaved by metathesis.[41] Considering our previous mechanism proposal for the Pd-independent dehalogenation reaction of the bromopyrazoles, we can offer the annular tautomerism again as a key phenomenon to explain the origin of the side protodeboronation reaction (Scheme 2). The prototropic shift at the ipso-position is promoted by the base. Subsequent irreversible reductive elimination of boric acid is driven by rearomatization leading to the phenolate anion. Cheon`s assumed formation of the ate complex can have the synergy effect to form the phenol 4*H*-tautomer. In contrast, 4-methoxyphenylboronic acid **3e** was stable under the same conditions, only a trace of anisole was detected after 2 hours. However, the protodeboronation of **3e** was significant after the prolonged reaction time (24%, 20 h), which can be attributed to other mechanisms.[41]



Scheme 2. Proposed protodeboronation mechanism of boronic acid **3f**.

Then, the attention was paid to the ortho-methoxy-substituted boronic acids **3g** and **3h**. Pyrazole **4g** was isolated in the good yield and, surprisingly, the reaction conditions also allowed to give tetra-ortho-substituted pyrazole **4h** in the yield of 84%, even the unprotected pyrazole was used (entries 7 and 8). This very good yield can be attributed to a lower steric hindrance of the methoxy groups in comparison to the methyl groups when boronic acid **3d** was used.[44] Further, the prolonged reaction time and an additional amount of boronic acid **3h** and XPhos Pd G2 was necessary to improve the yield. The larger methoxynaphthalene moiety did not affect negatively the yield of pyrazole **4i** (entry 9).

The lower reactivity of benzeneboronic acids **3j** and **3k** with the electron-withdrawing groups was overcome with an extra reaction time and amount of the corresponding boronic acid together with the catalyst to provide pyrazoles **4j** and **4k** in good to excellent yields (entries 10 and 11). In contrast, the styryl boronic acids **3l-3o** were not added in the excess and the coupling was finished within 20 h to yield the pyrazoles in a range 45-80% (entries 12-15).

In the end, the study was focused on the several heteroaryl boronic acids based on the thiophene and pyridine ring (entries 16-22). Thienyl-3-ylboronic acid and the corresponding pinacol ester **3p** gave pyrazole **4p** in a good yield, but isomer **3q** afforded only 30% of pyrazole **4q** although the boronic acid was used as a MIDA ester in the excess. Modification of thiophene with the ortho-fused benzene ring brought a better reactivity of boronic acids **3r** and **3s** giving bisheteroaryls **4r** and **4s** at the comparable yields with pyrazole **4p.** However, an extra addition of the corresponding boronic acids and the catalyst was necessary. Unfortunately, all attempts to react pyridineboronic acids or their MIDA or neopentylglycol esters with pyrazole **2** failed (entries 20-22).

Next, we sought for an efficient reduction method to convert the both nitro groups into the amine functionality. For this purpose, pyrazole **4a** was chosen as a model compound. Initially, from a broad spectrum of methods, we attempted to utilize the catalytic hydrogenation on 10% Pd/C under various conditions. Desired diaminopyrazole **5a** was always detected as a major compound in a reaction mixture, but also difficult to separate impurities were formed.

Consequently, we focused on the iron-catalyzed reduction with hydrazine as a hydrogen source reported by Shelev.[9] To reduce the both nitro groups and to avoid a potentially problematic isolation process after reduction, we modified the procedure and prepared the catalyst by deposition of 5% Fe on activated charcoal. This practical form of the catalyst allowed to give diaminopyrazoles **5a-5s** from the fair to excellent yields (Table 3). Only derivatives **5j**, **5l**, **5n**, and **5o** required additional chromatographic purification. No trends between the structure and the yield were identified.

Since the hydroxyl group in CAN508 is essential for the CDK inhibition,[6] it was important to develop a demethylation method for dinitropyrazole **3m** or diaminopyrazole **6m** to access desired carboanalog **1**. Preliminary demethylation attempts with the methoxy-substituted pyrazoles **4e** and **4i** showed the problematic use of boron tribromide and concentrated hydrobromic acid. The LCMS analyses revealed the complicated reaction mixtures containing brominated compounds. Demethylation occurred only with pyrazole **4e** if concentrated hydrobromic acid was used. The attempts with diaminopyrazole **5i** brought similar results together with the expected worse conversion of the starting material.

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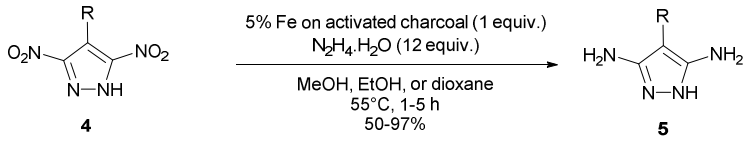
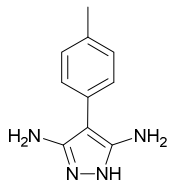
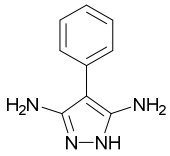
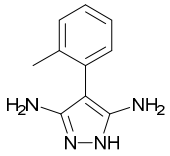
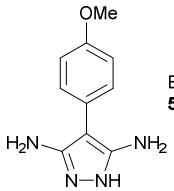
Table 3. Iron-catalyzed reduction of nitropyrazoles **4** into aminopyrazoles **5**.

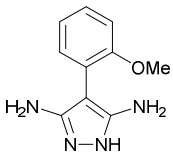


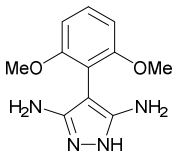

EtOH, 2 h
5a (79%)

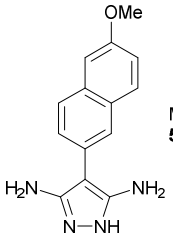

EtOH, 2 h
5b (83%)

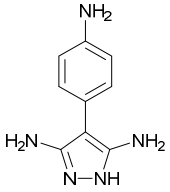

MeOH, 1 h
5c (62%)

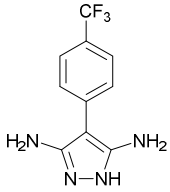

EtOH, 1 h
5e (85%)

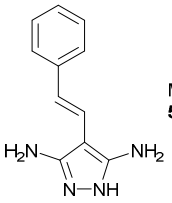

MeOH, 1 h
5g (82%)

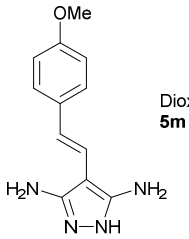

EtOH, 1h
5h (97%)

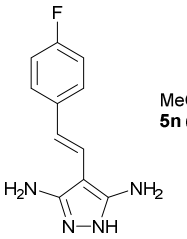

MeOH, 1 h
5i (86%)

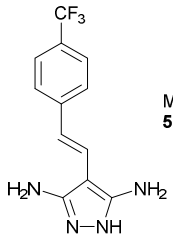

EtOH, 5 h
5j (51%)

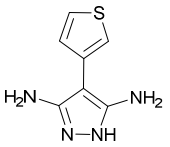

MeOH, 2 h
5k (97%)

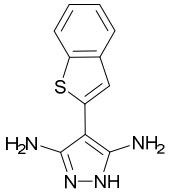

MeOH, 1h
5l (61%)

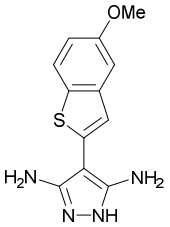

Dioxane, 3 h
5m (84%)


MeOH, 1 h
5n (51%)


MeOH, 2 h
5o (50%)


MeOH, 2 h
5p (80%)


MeOH, 1.5 h
5r (62%)


MeOH,1h
5s (64%)

Afterwards, the demethylation tactic was focused on sulfur reagents. The reactions with benzenethiol and 2-mercaptoethanol gave the desired demethylated product of pyrazole **5i** in the unsatisfactory yields. The better result was observed with sodium sulfide. However, the demethylation of **5i** with sodium ethanethiolate indicated more promising results. These conditions were utilized to provide pyrazole **1** (Scheme 3). The demethylation rate of pyrazole **5m** with sodium sulfide was fast. Nevertheless, it was necessary to terminate the reaction already after 1 hour, although the conversion of **5m** was not completed. The reason was a formation of a difficult to separate side product.

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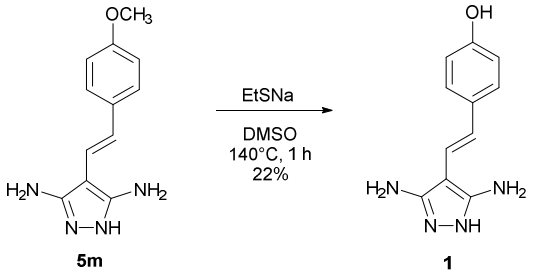

Scheme 3. Demethylation of **5m**.

Conclusions

In summary, we developed the general and efficient synthetic method, which enabled to provide the broad scope of 4-substituted-1*H*-pyrazole-3,5-diamines. The first step is based on the SMC reaction of pyrazole **2** with the boronic acids to provide aryl, heteroaryl, or styryl dinitropyrazoles **4**. The good results of the coupling reaction were provided primarily by the two factors: (a) The introduction of the electron-deficient nitro groups as a masked amino functionality, which improved the rate of the oxidative addition step and eliminated the Pd-independent side dehalogenation reaction, and (b) The utilization of the XPhos Pd G2 precatalyst, which enabled the coupling with the electron-deficient, -rich, or sterically demanding boronic acids. The subsequent general and practical iron-catalyzed reduction of the nitro groups with hydrazine hydrate accomplished the second step resulting in diaminopyrazoles **5**. Finally, desired carboanalog **1** was achieved by the demethylation with sodium ethanethiolate.

Experimental

4-Bromo-3,5-dinitro-1*H*-pyrazole (2)

Pyrazole (9.15 g, 0.134 mol) was dissolved in water (110 mL) and *N*-bromosuccinimide (23.9 g, 0.134 mol) was slowly added under continuous stirring and cooling to keep the temperature below 25 °C. The reaction mixture was then stirred for 30 min at room temperature followed by stirring and cooling for 30 min. White crystals were filtered-off and recrystallized from water.[33] Subsequently, 4-bromo-1*H*-pyrazole (10 g, 0.07 mol) was dissolved in 96% sulfuric acid (102 mL) and 98,5-99% fuming nitric acid (9 mL) was added dropwise at 100°C and stirred for 5 h. Then, the reaction mixture was poured into the ice, extracted with EtOAc, and collected organic layers were dried with $MgSO_4$. Ethyl acetate was evaporated under reduced pressure to get a crude product, which was recrystallized from water as a pale yellow solid (10.5 g, 65%); mp 167-169°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 14.38 (br. s., 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 150.4, 88.0. HRMS (ESI-TOF): calcd for $C_3BrN_4O_4$ $[M-H]^-$ 234.9103, found 234.9089.

General procedure for dinitropyrazoles 4: See Table 2. A mixture of pyrazole **2** (1.0 mmol), boronic acid **3** (1.05 mmol), and K_3PO_4 (848 mg, 4.0 mmol) was placed into a vial and suspended in dioxane (4 mL) and water (1 mL). The reaction mixture was degassed with argon for 15 min. Then, precatalyst XPhos Pd G2 (16 mg, 0.02 mmol) was added and the vial was quickly closed and inserted into an oil bath preheated to 100 °C. The mixture was vigorously stirred at 100 °C for 20 h. If pyrazole **2** was still observed, an additional amount of boronic acid and precatalyst XPhos Pd G2 was added (see Table 2). After pyrazole **2** was consumed, vial was pulled out from the oil bath and acidified by hydrochloric acid to reach pH 1. Then the solvent was evaporated under reduced pressure to dryness.

Isolation Method A: Water (40 mL) was added to the residue, resulting precipitate was filtered-off, and thoroughly washed with water. Wet precipitate of **4a**, **4b**, **4e**, **4i**, **4l** and **4o** was dissolved in MeOH (5-10 mL) or EtOAc (**4j, 4r**, **4n**, **4m** and **4s**), charcoal was added, and the suspension was stirred for 15 minutes at room temperature. Then, the suspension was filtered through Celite, the filter cake was washed with MeOH (EtOAc), and the filtrate was concentrated under reduced pressure. A crude product was applied on a silica gel column and eluted with hexane:EtOAc:MeOH (70:30:0 to 70:30:10) to give the desired dinitropyrazole **4** as a solid or oil. *Isolation Method B:* Water (30 mL) was added to the residue and a resulting mixture was extracted with EtOAc (3 × 20 mL). Collected organic layers were washed with water (20 mL) and dried over $MgSO_4$. After magnesium sulfate was filtered-off, charcoal was added, and the suspension was stirred for 15 minutes. After that, the suspension was filtered through Celite, the filter cake was washed with EtOAc, and the filtrate was concentrated under reduced pressure. A crude product was applied on a silica gel column and eluted with hexane:EtOAc:MeOH (70:30:0 to 70:30:10) to give the desired dinitropyrazole **4** as a solid or oil.

3,5-Dinitro-4-(*p*-tolyl)-1*H*-pyrazole (4a). *Isolation Method A*. A yellow solid (158 mg, 64% yield); mp > 340 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.35 (d, *J*=8.3 Hz, 2 H), 7.25 (d, *J*=8.3 Hz, 2 H), 2.37 (s, 3 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 148.2, 138.3, 129.8, 128.6, 124.0, 114.5, 21.0. HRMS (ESI-TOF): calcd for $C_{10}H_7N_4O_4$ $[M - H]^-$ 247.0467, found 247.0463.

3,5-Dinitro-4-phenyl-1*H*-pyrazole (4b). *Isolation Method A*. A pale yellow solid (153 mg, 65% yield); mp 170-176°C (DCM-hexanes). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.40 - 7.31 (m, 3 H), 7.31 - 7.36 (m, 2 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 152.7, 130.7, 129.8, 127.7, 127.4, 113.9. HRMS (ESI-TOF): calcd for $C_9H_5N_4O_4$ $[M - H]^-$ 233.0311, found 233.0305.

3,5-Dinitro-4-(*o*-tolyl)-1*H*-pyrazole (4c). *Isolation Method B*. A yellow solid (179 mg, 72% yield); mp 162-170 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.26 - 7.19 (m, 2 H), 7.14 (td, *J*=7.3, 2.7 Hz, 1 H), 7.04 (d, *J*=7.3 Hz, 1 H), 1.97 (s, 3 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 154.2, 136.3, 131.9, 129.3, 129.2, 127.2, 125.2, 113.1, 19.6. HRMS (ESI-TOF): calcd for $C_{10}H_7N_4O_4$ $[M - H]^-$ 247.0467 found 247.0463.

4-(4-Methoxyphenyl)-3,5-dinitro-1*H*-pyrazole (4e). *Isolation Method A*. A yellow solid (193 mg, 73% yield); mp 231-234 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.28 (d, *J*=8.8 Hz, 2 H), 6.95 (d, *J*=8.3 Hz, 2 H), 3.80 (s, 3 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 158.9, 151.7, 131.3, 121.4, 113.9, 113.2, 55.1 HRMS (ESI-TOF): calcd for $C_{10}H_7N_4O_5$ $[M - H]^-$ 263.0416 found 263.0415.

4-(2-Methoxyphenyl)-3,5-dinitro-1*H*-pyrazole (4g). *Isolation Method B*. A yellow solid (159 mg, 60% yield); mp 134-136 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.35 (t, *J*=7.8 Hz, 1 H), 7.26 (d, *J*=7.3 Hz, 1 H), 7.04 (d, *J*=8.3 Hz, 1 H), 6.97 (t, *J*=7.3 Hz, 1 H), 3.64 (s, 3 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 156.6, 152.0, 131.0, 129.5, 120.0, 118.6, 110.9, 110.0, 55.3.

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DOI: 10.1039/C7OB02373A

4-(2,6-Dimethoxyphenyl)-3,5-dinitro-1*H*-pyrazole (4h). *Isolation Method B*. A yellow solid (242 mg, 84% yield); mp 178-84 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.35 (t, *J*=8.6 Hz, 1 H), 6.72 (d, *J*=8.3 Hz, 2 H), 3.64 (s, 6 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 157.4, 151.0, 130.3, 106.2, 106.1, 104.1, 55.7. HRMS (ESI-TOF): calcd for $C_{11}H_9N_4O_6$ [M - H]$^-$ 293.0522, found 293.0521.

4-(6-Methoxynaphtalen-2-yl)-3,5-dinitro-1*H*-pyrazole (4i). *Isolation Method A*. A yellow solid (204 mg, 65% yield); mp 332-334 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.79 (d, *J*=8.7 Hz, 1 H), 7.78 (d, *J*=8.7 Hz, 1 H), 7.72 (d, *J*=1.0 Hz, 1 H), 7.38 - 7.30 (m, 2 H), 7.16 (dd, *J*=8.7, 2.5 Hz, 1 H), 3.89 (s, 3 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 157.4, 154.1, 133.4, 129.4, 128.7, 128.2, 128.1, 126.8, 125.8, 118.5, 114.0, 105.8, 55.3. HRMS (ESI-TOF): calcd for $C_{14}H_9N_4O_5$ [M-H]$^-$ 313.0573, found 313.0571.

3,5-Dinitro-4-(4-nitropenyl)-1*H*-pyrazole (4j). *Isolation Method A*. A yellow solid (209 mg, 75% yield); mp 150-152 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.22 (d, *J*=8.7 Hz, 2 H), 7.61 (d, *J*=8.7 Hz, 1 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 153.2, 146.6, 139.0, 131.3, 122.8, 111.8. HRMS (ESI-TOF): calcd for $C_9H_4N_5O_6$ [M - H]$^-$ 278.0162 found 278.0159.

3,5-Dinitro-4-(4-trifluoromethyl)phenyl)-1*H*-pyrazole (4k). *Isolation Method A*. A pale yellow solid (211 mg, 70% yield; 93% yield – from pinacol ester); mp 188-89 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.74 (d, *J*=8.2 Hz, 2 H), 7.57 (d, *J*=8.2 Hz, 2 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 152.5, 135.4, 130.7, 127.9 (q, *J*=32.6 Hz), 124.5 (q, *J*=3.8 Hz), 124.4 (q, *J*=272.2 Hz), 112.5. HRMS (ESI-TOF): calcd for $C_{10}H_4F_3N_4O_4$ [M - H]$^-$ 301.0185 found 301.0181.

(*E*)-3,5-Dinitro-4-styryl-1*H*-pyrazole (4l). *Isolation Method B*. An orange solid (162 mg, 62% yield); mp 336-338 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.56 (d, *J*=7.3 Hz, 2 H), 7.41 (t, *J*=7.3 Hz, 2 H), 7.38 - 7.28 (m, 2 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 151.2, 136.6, 136.4, 128.9, 128.5, 126.6, 114.9, 111.5. HRMS (ESI-TOF): calcd for $C_{11}H_7N_4O_4$ [M - H]$^-$ 259.0467, found 259.0465.

(*E*)-4-(4-Methoxystyryl)-3,5-dinitro-1*H*-pyrazole (4m).[9] *Isolation Method A*. A red solid (191 mg, 66% yield); mp 318-322 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.49 (d, *J*=8.8 Hz, 2 H), 7.32 (d, *J*=16.6 Hz, 1 H), 7.24 (d, *J*=16.6 Hz, 1 H), 6.97 (d, *J*=8.8 Hz, 2 H), 3.78 (s, 3 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 159.5, 152.4, 135.2, 129.6, 128.0, 114.3, 113.4, 111.7, 55.2. HRMS (ESI-TOF): calcd for $C_{12}H_9N_4O_5$ [M - H]$^-$ 289.0573, found 289.0572.

***(E)*-4-(4-Flourostyryl)-3,5-dinitro-*1H*-pyrazole (4n).** *Isolation Method A*. A brown solid (228 mg, 82% yield); mp 332-334 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.61 (dd, *J*=8.8, 5.7 Hz, 2 H), 7.35 (d, *J*=16.6 Hz, 1 H), 7.28 (d, *J*=16.6 Hz, 1 H), 7.23 (t, *J*=8.8 Hz, 2 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 162.1 (d, *J*=246.3 Hz), 151.7, 134.6, 133.4 (d, *J*=2.9 Hz), 128.6 (d, *J*=8.6 Hz), 115.8 (d, *J*=21.1 Hz), 115.8, 111.2. HRMS (ESI-TOF): calcd for $C_{11}H_6FN_4O_4$ [M - H]$^-$ 277.0373, found 277.0371.

***(E)*-3,5-Dinitro-4-(4-(trifluoromethyl)styryl)-1*H*-pyrazole (4o).** *Isolation Method A*. A yellow solid (148 mg, 45% yield); mp 318-322 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.75 (d, *J*=8.8 Hz, 2 H), 7.73 (d, *J*=8.8 Hz, 2 H), 7.57 (d, *J*=16.6 Hz, 1 H), 7.31 (d, *J*=16.6 Hz, 1 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 153.5, 141.3, 132.7, 127.8 (q, *J*=31.6 Hz), 127.0, 125.71 (q, *J*=3.8 Hz), 124.3 (q, *J*=272.2 Hz), 119.6, 110.1. HRMS (ESI-TOF): calcd for $C_{12}H_6F_3N_4O_4$ [M - H]$^-$ 327.0341, found 327.0339.

3,5-Dinitro-4-(thiophen-3-yl)-1*H*-pyrazole (4p). *Isolation Method B*. A brown solid (155 mg, 65% yield – from boronic acid and pinacol ester); mp 200-205 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.48 (dd, *J*=4.8, 3.0 Hz, 1 H), 7.44 (dd, *J*=2.7, 1.0 Hz, 1 H), 7.05 (dd, *J*=4.8, 1.1 Hz, 1 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 151.7, 129.5, 128.1, 126.0, 124.6, 109.0. HRMS (ESI-TOF): calcd for $C_7H_3N_4O_4S$ [M - H]$^-$ 238.9875, found 238.9870.

3,5-Dinitro-4-(thiophen-2-yl)-1*H*-pyrazole (4q). *Isolation Method B*, then crystallization from water. A brown-green solid (36 mg, 30% yield); mp 123-124 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.27 (br. s., 1 H), 7.77 (dd, *J*=5.0, 1.2 Hz, 1 H), 7.28 (dd, *J*=3.6, 1.2 Hz, 1 H), 7.16 (dd, *J*=4.7, 3.6 Hz, 1 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 149.2, 130.8, 129.0, 127.0, 125.7, 107.4. HRMS (ESI-TOF): calcd for $C_7H_3N_4O_4S$ [M - H]$^-$ 254.9824, found 238.9871.

4-(Benzo[*b*]thiophen-2-yl)-3,5-dinitro-1*H*-pyrazole (4r). *Isolation Method B*. A brown solid (179 mg, 62% yield); mp 310-314 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.00 - 7.93 (m, 1 H), 7.88 - 7.80 (m, 1 H), 7.43 - 7.32 (m, 3 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 153.3, 140.1, 139.3, 131.1, 125.2, 124.4, 124.3, 123.7, 122.2, 105.8. HRMS (ESI-TOF): calcd for $C_{11}H_5N_4O_4S$ [M - H]$^-$ 289.0032, found 289.0030.

4-(5-Methoxybenzo[*b*]thiophen-2-yl)-3,5-dinitro-1*H*-pyrazole (4s). *Isolation Method A*. A dark brown oil (112 mg, 70% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.80 (d, *J*=8.8 Hz, 1 H), 7.37 (d, *J*=2.6 Hz, 1 H), 7.25 (s, 1 H), 6.99 (dd, *J*=8.8, 2.6 Hz, 1 H), 3.82 (s, 3 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 157.0, 154.5, 140.6, 133.5, 132.3, 124.5, 122.8, 114.3, 105.8, 105.4, 55.3. HRMS (ESI-TOF): calcd for $C_{12}H_7N_4O_5S$ [M - H]$^-$ 319.0137, found 319.0134.

General procedure for diaminopyrazoles 5: Pyrazole **4** (1 equiv.) was dissolved in ethanol, methanol, or dioxane (see Table 3). A catalyst (5% Fe on activated charcoal, see the following procedure) and hydrazine hydrate (12 equiv.) was added and the resulting suspension was heated to 55°C in on oil bath. The reduction was monitored by TLC ($CHCl_3$:MeOH 10:1). After dinitropyrazole **4** was completely reduced, the catalyst was filtered-off through Celite, resulting filtrate was filtered through a microfilter, and solvent was evaporated under reduced pressure to give a crude product. If necessary, pyrazoles were purified by flash chromatography ($CHCl_3$:MeOH from 30:1 to 5:1).

Preparation of the catalyst (5% Fe on activated charcoal)

Iron(II) sulfate heptahydrate (1.24 g, 4.4 mmol) was dissolved in water (20 mL). The solution was acidified with one drop of conc. sulfuric acid, diluted with another two portions of water (2 × 20 mL), and activated charcoal (4.75 g) was added. Hydrazine hydrate (0.5 mL, 10.3 mmol) was added to the suspension, which was continuously stirred at room temperature for 1 minute. Then, the temperature was increased to 100 °C and the suspension was boiled for 5 minute. After that, the suspension was allowed to cool to room temperature. The catalyst was filtered-off, washed with water, and dried on air.

4-(*p*-Tolyl)-1*H*-pyrazole-3,5-diamine (5a).[43] Title product **5a** was prepared under General procedure, pyrazole **4a** (112 mg, 0.45 mmol), EtOH (4.5 mL), catalyst 5% Fe on activated charcoal (503 mg, 0.45 mmol), $N_2H_4{\cdot}H_2O$ (264 µl, 5.4 mmol), 2 h. Beige solid (67 mg, 79% yield); mp 182-188°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.22 (br. s., 1H), 7.25 (d, *J* = 7.8 Hz, 2H), 7.13 (d, *J* = 7.8 Hz, 2H), 4.48 (br. s, 4H), 2.28 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 148.3,

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DOI: 10.1039/C7OB02373A

132.7, 131.5, 129.1, 126.7, 90.1, 20.7. HRMS (ESI-TOF): calcd for $C_{10}H_{13}N_4$ $[M + H]^+$ 189.1140, found 189.1135.

4-Phenyl-1*H*-pyrazole-3,5-diamine (5b).[43] Title product **5b** was prepared under General procedure, pyrazole **4b** (70 mg, 0.32 mmol), EtOH (3.0 mL), catalyst 5% Fe on activated charcoal (335 mg, 0.32 mmol), $N_2H_4{\cdot}H_2O$ (174 µl, 3.6 mmol), 1 h. White solid (43 mg, 83% yield); mp 206-210°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.32 (br. s., 1 H), 7.37 (d, *J*=7.8 Hz, 1 H), 7.32 (t, *J*=7.3 Hz, 2 H), 7.08 (t, *J*=7.3 Hz, 1 H), 4.50 (br. s., 4 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 148.3, 134.6, 128.5, 126.6, 123.7, 90.4. HRMS (ESI-TOF): calcd for $C_9H_{11}N_4$ $[M + H]^+$ 175.0984, found 175.0979.

4-(*o*-(Tolyl)-1*H*-pyrazole-3,5-diamine (5c).[43] Title product **5c** was prepared under General procedure, pyrazole **4c** (82 mg, 0.33 mmol), MeOH (2.5 mL), catalyst 5% Fe on activated charcoal (367 mg, 0.33 mmol), $N_2H_4{\cdot}H_2O$ (195 µl, 3.98 mmol), 1 h. The product **5c** was purified via a column chromatography to yield title product as pale yellow oil (39 mg, 62% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.89 (br. s, 1 H), 7.20 - 7.26 (m, 1 H), 7.09 - 7.18 (m, 3 H), 4.18 (br. s, 4 H), 2.20 (s, 3 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 148.4, 137.3, 132.6, 131.0, 130.1, 126.0, 125.5, 90.1, 19.8. HRMS (ESI-TOF): calcd for $C_{10}H_{13}N_4$ $[M + H]^+$ 189.1140, found 189.1135.

4-(4-Methoxyphenyl)-1*H*-pyrazole-3,5-diamine (5e).[43] Title product **5e** was prepared under General procedure, pyrazole **4e** (92 mg, 0.35 mmol), EtOH (3.0 mL), catalyst 5% Fe on activated charcoal (389 mg, 0.35 mmol), $N_2H_4{\cdot}H_2O$ (202 µl, 4.2 mmol), 1 h. Beige solid (59 mg, 85% yield); mp 220-222°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.05 (br. s, 1 H), 7.27 (d, *J*=8.8 Hz, 2 H), 6.91 (d, *J*=8.8 Hz, 2 H), 4.42 (br. s., 4 H), 3.74 (s, 3 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 156.2, 148.6, 128.1, 126.8, 114.1, 90.1, 55.0. HRMS (ESI-TOF): calcd for $C_{10}H_{13}N_4O$ $[M + H]^+$ 205.1089, found 205.1085.

4-(2-Methoxyphenyl)-1*H*-pyrazole-3,5-diamine (5g).[43] Title product **5g** was prepared under General procedure, pyrazole **4g** (102 mg, 0.39 mmol), MeOH (5.0 mL), catalyst 5% Fe on activated charcoal (431 mg, 0.39 mmol), $N_2H_4{\cdot}H_2O$ (135 µl, 4.63 mmol), 1 h. The products **5g** was purified via a column chromatography to yield title product as a pale yellow oil (56 mg, 82% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.26 (br. s, 1 H), 7.24 (dd, *J*=7.3, 1.6 Hz, 1 H), 7.17 (td, *J*=7.3, 2.1 Hz, 1 H), 7.01 (dd, *J*=8.3, 1.0 Hz, 1 H), 6.94 (td, *J*=7.3, 1.0 Hz, 1 H), 4.24 (br. s, 4 H), 3.78 (s, 3 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 155.6, 148.7, 129.8, 126.3, 122.6, 120.6, 111.4, 87.7, 55.3. HRMS (ESI-TOF): calcd for $C_{10}H_{13}N_4O$ $[M + H]^+$ 205.1089, found 205.1085.

4-(2,6-Dimethoxyphenyl))-1*H*-pyrazole-3,5-diamine (5h). Title product **5h** was prepared under General procedure, pyrazole **4h** (181 mg, 0.61 mmol), EtOH (5.0 mL), catalyst 5% Fe on activated charcoal (686 mg, 0.61 mmol), $N_2H_4{\cdot}H_2O$ (360 µl, 7.4 mmol), 1 h. Yellow solid (139 mg, 97 % yield); mp 83-86°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.19 (t, *J* = 8.3 Hz, 1H), 6.67 (d, *J* = 8.3 Hz, 2H), 4.02 (br. s), 3.74 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 157.1, 149.4, 127.2, 110.3, 104.2, 84.0, 55.5. HRMS (ESI-TOF): calcd for $C_{11}H_{15}N_4O_2$ $[M + H]^+$ 235.1195, found 235.1190.

4-(6-Methoxynaphtalen-2-yl)-1*H*-pyrazole-3,5-diamine (5i). Title product **5i** was prepared under General procedure, pyrazole **4i** (100 mg, 0.32 mmol), MeOH (10.0 mL), catalyst 5% Fe on activated charcoal (357 mg, 0.32 mmol), $N_2H_4{\cdot}H_2O$ (185 µl, 3.8 mmol), 1 h. Pale yellow solid (70 mg, 86% yield); mp 220-226°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.40 (br. s., 1 H), 7.75 (t, *J*=8.3 Hz, 1 H), 7.73 (s, 1 H), 7.58 (dd, *J*=8.6, 1.3 Hz, 1 H), 7.25 (d, *J*=2.1 Hz, 1 H), 7.11 (dd, *J*=8.8, 2.6 Hz, 1 H), 4.84 (br. s, 2 H), 4.32 (br. s, 2 H), 3.86 (s, 3 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 156.4, 152.1, 131.5, 129.8, 129.1, 128.9, 126.7, 126.6, 124.0, 118.2, 105.7, 90.4, 55.1. HRMS (ESI-TOF): calcd for $C_{14}H_{15}N_4O$ $[M + H]^+$ 255.1246, found 255.1241.

4-(4-Aminophenyl)-1*H*-pyrazole-3,5-diamine (5j). Title product **5j** was prepared under General procedure, pyrazole **4j** (178 mg, 0.64 mmol), EtOH (7.0 mL), catalyst 5% Fe on activated charcoal (715 mg, 0.64 mmol), $N_2H_4{\cdot}H_2O$ (560 µl, 11.52 mmol), 5 h. The products **5j** was purified via a column chromatography to yield title product as a bright brown solid (62 mg, 51% yield); mp 186-188°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.22 (br. s., 1 H), 7.00 (d, *J*=8.3 Hz, 2 H), 6.57 (d, *J*=8.3 Hz, 2 H), 4.85 (s, 2 H), 4.26 (br. s., 4 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 146.0, 145.4, 127.9, 121.7, 114.4, 90.8. HRMS (ESI-TOF): calcd for $C_9H_{12}N_5$ $[M + H]^+$ 190.1093, found 190.1088.

4-(4-(Trifluoromethyl)phenyl)-1*H*-pyrazole-3,5-diamine (5k). Title product **5k** was prepared under General procedure, pyrazole **4k** (66 mg, 0.21 mmol), MeOH (3.0 mL), catalyst 5% Fe on activated charcoal (242 mg, 0.21 mmol), $N_2H_4{\cdot}H_2O$ (125 µl, 2.52 mmol), 2 h. Pale yellow solid (50 mg, 97% yield); mp 160-162°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.61 (br. s, 1 H), 7.62 (d, *J*=9.3 Hz, 2 H), 7.59 (d, *J*=9.3 Hz, 2 H), 4.74 (br. s., 4 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 149.1, 139.3, 126.4, 125.1 (q, *J*=3.8 Hz), 123.4 (q, *J*=32.6 Hz), 124.8 (q, *J*=270.3 Hz), 89.5. HRMS (ESI-TOF): calcd for $C_{10}H_{10}F_3N_4$ $[M + H]^+$ 243.0858, found 243.0852.

(*E*)-4-Styryl-1*H*-pyrazole-3,5-diamine (5l). Title product **5l** was prepared under General procedure, pyrazole **4l** (114 mg, 0.44 mmol), MeOH (7.0 mL), catalyst 5% Fe on activated charcoal (488 mg, 0.44 mmol), $N_2H_4{\cdot}H_2O$ (255 µl, 5.2 mmol), 1 h. The products **5l** was purified via a column chromatography to yield title product as a white solid (53 mg, 61% yield) ; mp 212-214°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.16 (br. s., 1 H), 7.42 (d, *J*=7.3 Hz, 2 H), 7.26 (t, *J*=7.3 Hz, 1 H), 7.06 (t, *J*=7.3 Hz, 1 H), 7.03 (d, *J*=16.6 Hz, 1 H), 6.45 (d, *J*=16.6 Hz, 1 H), 4.92 (br. s., 1 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 149.7, 139.9, 128.3, 124.9, 124.7, 120.6, 117.9, 88.9. HRMS (ESI-TOF): calcd for $C_{11}H_{13}N_4$ $[M + H]^+$ 201.1140, found 201.1135.

(*E*)-4-(4-Methoxystyryl)-1*H*-pyrazole-3,5-diamine (5m). Title product **5m** was prepared under General procedure, pyrazole **4m** (235 mg, 0.81 mmol), dioxane (16.0 mL), catalyst 5% Fe on activated charcoal (905 mg, 0.415 mmol), $N_2H_4{\cdot}H_2O$ (475 µl, 9.7 mmol), 3 h. Yellow solid (157 mg, 84 % yield); mp 190-194°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.35 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 16.6 Hz, 1H), 6.40 (d, *J* = 16.6 Hz, 1H), 4.44 - 5.26 (m, 4H), 3.73 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 157.1, 149.5, 132.6, 125.8, 118.5, 118.0, 113.9, 88.8, 55.0 HRMS (ESI-TOF): calcd for $C_{12}H_{15}N_4O$ $[M + H]^+$ 231.1246, found 231.1241.

(*E*)-4-(4-Fluorostyryl)-1*H*-pyrazole-3,5-diamine (5n). Title product **5n** was prepared under General procedure, pyrazole **4n** (162 mg, 0.584 mmol), MeOH (6.0 mL), catalyst 5% Fe on activated charcoal (652 mg, 0.584 mmol), $N_2H_4{\cdot}H_2O$ (340 µl, 7.0 mmol), 1 h. The products **5n** was purified via a column chromatography to yield title product as a white solid (64 mg, 51 % yield); mp 192-198°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.23 (br. s, 1 H), 7.44 (dd, *J*=8.8, 5.7 Hz, 2 H), 7.09 (t, *J*=8.8 Hz, 2 H), 6.97 (d, *J*=16.6 Hz, 1 H), 6.44 (d, *J*=16.6 Hz, 1 H), 4.89 (br. s., 4 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 160.14 (d, *J*=240.6 Hz, 1 C), 149.69, 136.49 (d, *J*=2.9 Hz, 4 C), 126.11 (d, *J*=7.7

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Hz, 5 C), 120.53, 116.75, 115.09 (d, *J*=21.1 Hz, 6 C), 88.74. HRMS (ESI-TOF): calcd for $C_{11}H_{12}FN_4$ $[M + H]^+$ 219.1046, found 219.1041.

(*E*)-4-(4-(Trifluoromethyl)styryl)-1*H*-pyrazole-3,5-diamine (5o). Title product **5o** was prepared under General procedure, pyrazole **4o** (95 mg, 0.289 mmol), MeOH (3.0 mL), catalyst 5% Fe on activated charcoal (323 mg, 0.289 mmol), $N_2H_4 \cdot H_2O$ (170 µl, 3.5 mmol), 2 h. The products **6o** was purified via a column chromatography to yield title product as a pale yellow solid (39 mg, 50 % yield); mp 190-196°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.34 (br. s, 1H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.58 - 7.65 (m, 2H), 7.58 (d, *J* = 8.8 Hz, 2H), 7.25 (d, *J* = 16.6 Hz, 1H), 6.51 (d, *J* = 16.6 Hz, 7H), 5.05 (br. s., 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 150.2, 144.3, 125.2 (q, *J*=3.8 Hz), 124.7, 124.5 (q, *J*=31.6 Hz), 123.7, 124.7 (q, *J*=270.3 Hz), 115.72, 89.0. HRMS (ESI-TOF): calcd for $C_{12}H_{12}F_3N_4$ $[M + H]^+$ 269.1014, found 269.1010.

4-(Thiophen-3-yl)-1*H*-pyrazole-3,5-diamine (5p). Title product **5p** was prepared under General procedure, pyrazole **4p** (60 mg, 0.25 mmol), MeOH (2.0 mL), catalyst 5% Fe on activated charcoal (280 mg, 0.25 mmol), $N_2H_4 \cdot H_2O$ (147 µl, 3.0 mmol), 2 h. Yellow solid (36 mg, 80 % yield); mp 192-196°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.51 (dd, *J*=5.0, 2.7 Hz, 1 H), 7.33 (dd, *J*=5.0, 1.4 Hz, 1 H), 7.23 (dd, *J*=2.7, 1.4 Hz, 1 H), 4.62 (br. s., 4 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 148.3, 134.3, 126.7, 125.0, 116.0, 87.3 HRMS (ESI-TOF): calcd for $C_7H_9N_4S$ $[M + H]^+$ 181.0548, found 181.0543.

4-(Benzo[*b*]thiophen-2-yl)-1*H*-pyrazole-3,5-diamine (5r). Title product **5r** was prepared under General procedure, pyrazole **4r** (87 mg, 0.3 mmol), MeOH (6.0 mL), catalyst 5% Fe on activated charcoal (334 mg, 0.3 mmol), $N_2H_4 \cdot H_2O$ (175 µl, 3.6 mmol), 1.5 h. Yellow solid (43 mg, 62 % yield); mp 224-226°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.59 (br. s, 1 H), 7.83 (d, *J*=8.3 Hz, 1 H), 7.67 (d, *J*=7.8 Hz, 1 H), 7.30 (t, *J*=7.3 Hz, 1 H), 7.23 (s, 1 H), 7.20 (t, *J*=7.3 Hz, 1 H), 4.82 (br. s., 4 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 149.5, 140.6, 137.1, 136.8, 124.2, 122.5, 121.9, 121.7, 115.7, 86.1. HRMS (ESI-TOF): calcd for $C_{11}H_{11}N_4S$ $[M + H]^+$ 231.0704, found 231.0700.

4-(5-Methoxybenzo[*b*]thiophene-2-yl)-1*H*-pyrazole-3,5-diamine (5s). Title product **5s** was prepared under General procedure, pyrazole **4s** (77 mg, 0.24 mmol), MeOH (4.0 mL), catalyst 5% Fe on activated charcoal (268 mg, 0.24 mmol), $N_2H_4 \cdot H_2O$ (140 µl, 2.9 mmol), 1 h. Beige solid (40 mg, 64 % yield); mp 210°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.65 (br. s, 1 H), 7.69 (d, *J*=8.3 Hz, 1 H), 7.20 (d, *J*=2.1 Hz, 1 H), 7.16 (s, 1 H), 6.81 - 6.86 (m, 1 H), 4.88 (br. s, 4 H), 3.79 (s, 4 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 157.1, 148.6, 141.8, 138.2, 128.9, 122.4, 115.7, 112.0, 104.7, 86.2, 55.2. HRMS (ESI-TOF): calcd for $C_{12}H_{13}N_4OS$ $[M + H]^+$ 261.0810, found 261.0806.

4-(2-(3,5-Diamino-1*H*-pyrazol-4-yl)vinyl)phenol (1). Pyrazole **5m** (210 mg, 0.87 mmol) was dissolved in 12 mL DMSO, EtSNa (1.5 g, 17.5 mmol) was added, the vial inserted into an oil bath preheated to 140°C and the mixture was vigorously stirred for 1 h. Then the mixture was added into water (3 mL), neutralized by NH_4Cl and the product was then purified by column chromatography ($CHCl_3$:MeOH 40-5:1) immediately. Beige solid (42 mg, 22 % yield); m.p. 182-188°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.22 (br. s., 1 H), 7.23 (d, *J*=8.2 Hz, 2 H), 6.77 (d, *J*=16.6 Hz, 1 H), 6.68 (d, *J*=8.7 Hz, 2 H), 6.36 (d, *J*=16.6 Hz, 1 H), 4.90 (br. s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 155.3, 149.5, 130.9, 125.9, 118.8, 117.4, 115.2, 88.8. HRMS (ESI-TOF): calcd for $C_{11}H_{13}N_4O$ $[M + H]^+$ 216.1089, found 217.1085.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by the Czech National Program for Sustainability (project LO1304), the Operational Programme Enterprise and Innovations for Competitiveness (project CZ.01.1.02/0.0/0.0/15_019/0004431), and the internal Palacky University IGA projects (IGA_PrF_2017_009 and IGA_LF_2017_028).

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